Title Page

Protocol Title: A Phase 2b/c, Multi-Arm, 2-Stage, Duration Randomized Trial of the Efficacy and Safety of Two to Four Months Treatment with Regimens Containing Bedaquiline, OPC-167832, and Sutezolid, Plus Either Pretomanid or Delamanid, in Adults with Pulmonary Tuberculosis.

Protocol Number: Gates MRI-TBD06-201

NCT Number: NCT05971602

Original Protocol (Version 1.0): 27 Jun 2022

Amendment 1 (Version 2.0): 13 Oct 2022

Amendment 2 (Version 3.0): 06 Feb 2024

Regimen Name: Regimen 1 as delamanid, bedaquiline, OPC-167832 and sutezolid (DBOS) and Regimen 2 as pretomanid, bedaquiline, OPC-167832, and sutezolid (PBOS)

Trial Phase: Phase 2b/c

Short Title: Two-staged (Phase 2b/c), randomized duration-response efficacy and safety evaluation of two to four months of treatment with the combination regimens of DBOS and PBOS in adults with pulmonary tuberculosis

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Principal Investigator Signature Page

I have read the protocol, appendices, and accessory materials related to the Gates MRI-TBD06-201 trial entitled "A Phase 2b/c, Multi-Arm, 2-Stage, Duration Randomized Trial of the Efficacy and Safety of Two to Four Months Treatment with Regimens Containing Bedaquiline, OPC-167832, and Sutezolid, Plus Either Pretomanid or Delamanid, in Adults with Pulmonary Tuberculosis", and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with:
    - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - current International Council for Harmonization Guideline for Good Clinical Practice (GCP)
    - applicable laws and regulations
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain study records of each participant and all data required by the protocol.

_____ _____

Principal Investigator Signatory **Date**

Name:

Title:

Affiliation:

City and Country:

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List of Abbreviations

AE	Adverse Event(s)
AIDS	Acquired Immune Deficiency Syndrome
ATP	Adenosine Triphosphate
AESI	Adverse Event of Special Interest
ART	Antiretroviral treatment
BID	Bis in die (Latin for twice daily)
BPaL	Bedaquiline, Pretomanid, and Linezolid
CFU	Colony Forming Units
COVID-19	Coronavirus Disease caused by SARS-CoV-2 infection-19
DBOS	Delamanid, Bedaquiline, OPC-167832 and Sutezolid
DDI	Drug-drug interactions
DprE1	Deca-prenylphosphoryl-β-D-ribose 2′-epimerase 1
DS	Drug Sensitive
DS-TB	Drug Sensitive Tuberculosis
EBA	Early Bactericidal Activity
ECG	Electrocardiogram
EMA	European Medicines Agency
ET	Early Termination
FDA	United States Food and Drug Administration
FOCBP	Female of Child Bearing Potential
Gates MRI	Bill & Melinda Gates Medical Research Institute
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HFS-TB	Hollow Fiber System Model of Tuberculosis
HIV	Human Immunodeficiency Virus
HRZE or 2HRZE/4HR	Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) – refers to standard regimen of 8 weeks of HRZE followed by 18 weeks of HR
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INH	Isoniazid
IRB	Institutional Review Board
IRE	Infusion Related Event
[redacted]	[redacted]
MAO	Monoamine Oxidase
MAOI	Monoamine Oxidase Inhibitor
[redacted]	[redacted]
MDR	Multi-drug Resistant
MDR-TB	Multi-drug Resistant Tuberculosis
mg	Milligrams
MGIT	Mycobacteria Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
mITT	modified Intention to Treat

List of Abbreviations

mL	milliLiter
Mtb	Mycobacterium tuberculosis
NI	non-inferiority
NIH	National Institutes of Health
NOAEL	No-Observed-Adverse-Effect Level
PA	Posterior-Anterior
PBOS	Pretomanid, Bedaquiline, OPC-167832 and Sutezolid
[redacted]	
PK	Pharmacokinetics
PTR	Poor Treatment Response
QD	Quaque Die (Latin for once a day)
QTcF	QT interval corrected using Fridericia's formula
RMM	Relapsing Mouse Model
RNA	Ribonucleic Acid
RR-TB	Rifampicin resistant TB
RS	Ribonucleic Acid Synthesis
SAE	Serious Adverse Event(s)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCC	Sputum culture conversion
SD	Standard deviation
SoA	Schedule of Activities
SOC	Standard of Care
STrAW	Stop treatment and watch
TB	Tuberculosis
TI/NR	Treatment intolerant or non-responsive
µg	Microgram
ULN	Upper limit of normal
WHO	World Health Organization
XBOS	Regimen from Stage 1 that advances to Stage 2
XDR-TB	Extensively Drug Resistant Tuberculosis

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2b/c, Multi-Arm, 2-Stage, Duration Randomized Trial of the Efficacy and Safety of Two to Four Months Treatment with Regimens Containing Bedaquiline, OPC-167832, and Sutezolid, Plus Either Pretomanid or Delamanid, in Adults with Pulmonary Tuberculosis

Short Title: Two-staged (Phase 2b/c), randomized duration-response efficacy and safety evaluation of two to four months of treatment with the combination regimens of DBOS and PBOS in adults with pulmonary tuberculosis.

Overall Goals: To assess the efficacy, safety, optimal duration, and pharmacokinetics (PK) of Delamanid, Bedaquiline, OPC-167832, and Sutezolid (DBOS) and Pretomanid, Bedaquiline, OPC-167832, and Sutezolid (PBOS) in adult participants with drug sensitive tuberculosis (TB) and rifampicin or multi-drug resistant TB (RR/MDR-TB).

1.2. Rationale

Approximately one-fourth of the world's population is estimated to have *Mycobacterium tuberculosis* (*M. tuberculosis*; Mtb) infection and is at risk of developing active TB. Among those infected, approximately 10 million people develop active TB each year. In 2020, 1.5 million people died from TB, making it among the leading infectious disease killers in the world (World Health Organization [WHO], 2021a). With the global coronavirus disease-2019 (COVID-19) pandemic resulting in substantial disruptions to TB health services and the consequent increase in vulnerability to TB, TB incidence, and especially TB mortality, the WHO estimates that one-half million more people may have died from TB in 2020 alone due to the negative effects of the pandemic on global TB control. TB incidence and mortality are projected to increase by around 5% to 15% through 2025, amounting to hundreds of thousands of additional TB deaths worldwide (McQuaid et al, 2021).

The current recommended standard of care (SOC) for treating adults with drug-sensitive (DS) TB consists of an intensive phase of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by a continuation phase of 4 months of isoniazid and rifampicin (2HRZE/4HR); this treatment regimen was first introduced as the SOC more than 40 years ago (WHO, 2017a; Nahid et al, 2016). Though highly efficacious, several key issues are associated with administering this regimen effectively on a global scale. Among them, the duration and complexity of 2HRZE/4HR and its toxicities frequently result in nonadherence leading to suboptimal response (with treatment failure and relapse) and emergence of resistance, including multi-drug resistant (MDR) Mtb strains resistant to at least isoniazid and rifampicin – with on-going transmission of the disease (WHO, 2017a). The treatment increases in complexity and duration (up to 18 months in length) for patients infected with rifampicin-resistant (RR)/MDR Mtb strains (WHO, 2020). Drug-drug interactions caused by rifampicin's potent induction of cytochrome P450 enzymes is another major challenge with the 2HRZE/4HR regimen, particularly for women on hormonal contraception and TB patients co-infected with HIV taking antiretrovirals.

Although steady progress has been made over the past two decades in controlling the global TB pandemic and reducing annual incidence rates and deaths, there remains an urgent need for the

development of new potent anti-TB agents and combination regimens with low toxicity that are effective against all Mtb strains that can greatly reduce the duration required for treatment and decrease the need for costly and time-consuming drug sensitivity testing (Verguet et al, 2017). These new regimens with shorter treatment requirements will be essential for combating the losses incurred in TB control as a result of the global COVID-19 pandemic.

In recent years, three new anti-TB drugs, bedaquiline (Sirturo®) developed by Janssen, delamanid (Deltyba™) developed by Otsuka Pharmaceutical Co, Ltd (Otsuka), and pretomanid developed as part of a combination regimen including bedaquiline and linezolid by the TB Alliance, were evaluated and approved by stringent regulatory bodies. Bedaquiline is approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as part of combination treatment for adults and children (≥5 years and ≥15 kg) with pulmonary MDR-TB. Delamanid is approved by the EMA as part of combination treatment for adults, children, and infants (≥10 kg) for pulmonary MDR-TB. Pretomanid is approved by the FDA and the EMA for use in combination with bedaquiline and linezolid for adults with treatment-intolerant or non-responsive (TI/NR) MDR-TB and extensively drug resistant TB (XDR-TB), defined at the time of approval as MDR-TB with additional resistance to fluoroquinolones and injectable anti-TB agents. More details on the efficacy and safety of the three marketed products for treatment of MDR-TB are available in Section 3 and their respective product labels (Sirturo® Product Label, 2023; Deltyba™ Summary of Product Characteristics [SmPC, 2023]; Pretomanid Product Label, 2022; Dovprela™ Summary of Product Characteristics [SmPC, 2023]).

In addition, the pipeline of investigational agents in clinical development for TB treatment, including those with novel mechanisms of action, has continued to expand, and many – including sutezolid and Otsuka's OPC-167832 – are available to bring into combination regimen development with the newly approved anti-TB drugs to improve treatment options (Lee et al, 2012; Lee et al, 2015). Administered in combination, these new drugs have the potential to form the backbone of novel oral anti-TB drug regimens that may be able to substantially shorten the treatment for all forms of pulmonary TB regardless of the resistance profile (ie, "pan-TB" regimens).

1.2.1. Proposed Treatment Regimens

The two proposed treatment regimens for this Phase 2 clinical trial: delamanid, bedaquiline, OPC-167832, and sutezolid (DBOS, Regimen 1), and pretomanid, bedaquiline, OPC-167832, and sutezolid (PBOS, Regimen 2) have not yet been tested in a clinical trial. However, their evaluation is supported by the totality of the available nonclinical and clinical data on bedaquiline, delamanid, pretomanid, OPC-167832, and sutezolid administered as individual agents and as part of other combinations.

The combination of bedaquiline and pretomanid has been extensively evaluated in the development of pretomanid (Gils, 2021). The 3-drug regimen of bedaquiline, pretomanid, and linezolid formed the basis of pretomanid's regulatory approval, and represents 3 of the 4 drug classes proposed in the current trial (See Section 3.3.2.2.1). Similarly, the "end TB" prospective observational cohort study provides supportive evidence for the potential efficacy from the combined use of delamanid, bedaquiline, and linezolid as an agent from the oxazolidinone class

(See Section 3.3.1.1.1). Bedaquiline was also evaluated in a combination drug-drug interaction and safety trial with delamanid in MDR-TB patients (Dooley et al, 2021). The results demonstrated that QT interval prolongation using corrected Fridericia's formula (QTcF) of bedaquiline combined with delamanid was not more than additive and no participant experienced Grade 3 or 4 QTcF prolongation-related AEs.

Both sutezolid and OPC-167832 have demonstrated safety and efficacy in nonclinical studies and Phase 1 and Phase 2a clinical trials that support their inclusion in the proposed regimens. OPC-167832 in combination with delamanid or bedaquiline may have additive effects on bactericidal activity (OPC-167832 Investigator's Brochure, 2024). Sutezolid is a thiomorpholine analog of linezolid that exhibits in vitro potency against drug-sensitive and -resistant Mtb strains and improved bactericidal activity in mouse models of TB, including increased sterilizing activity over linezolid in combination with bedaquiline and pretomanid. Recently, Gates MRI completed 4-month and 6-month toxicology studies of sutezolid in monkeys and rats, respectively, which support 4 months of treatment in humans at the Phase 2a early bactericidal activity (EBA) trial's efficacious dose of 1200 mg QD. Developmental and reproductive toxicology studies in mice, rats, and rabbits have also been completed; the definitive studies support use of sutezolid in clinical studies enrolling women of child-bearing potential with appropriate measures to prevent pregnancy and informed consent to trial participants, and exclusion criteria for pregnancy and breastfeeding (see Section 3.2).

1.3. Trial Design

The trial will implement a two-staged Phase 2b/Phase 2c design (see Figure 1).

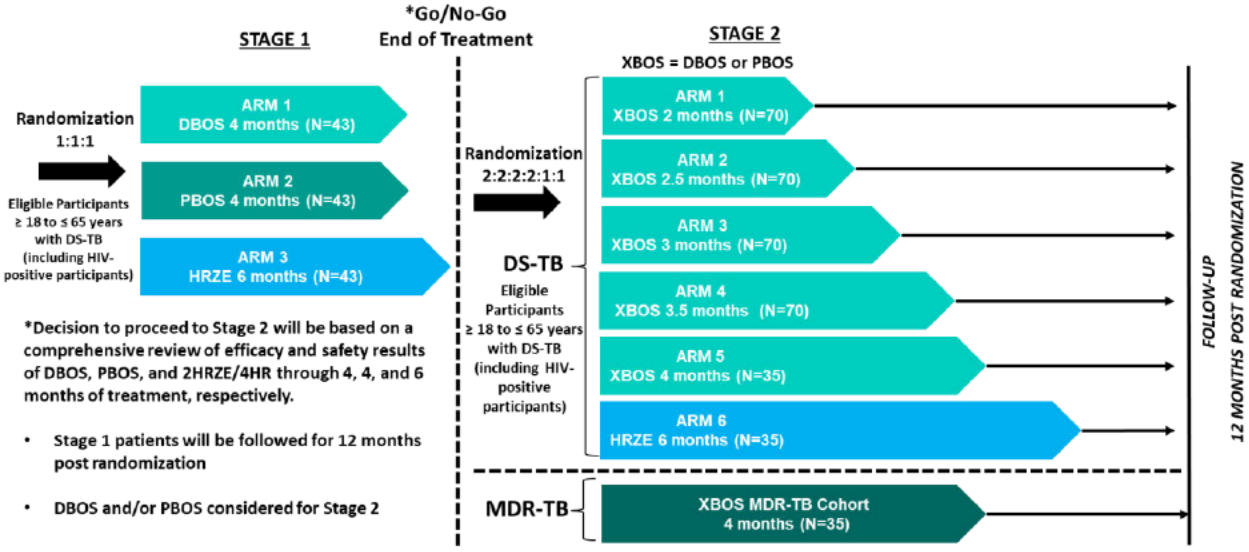
In Stage 1, the safety, tolerability, efficacy, and pharmacokinetics (PK) of DBOS and PBOS administered daily for 4 months (17 weeks) will be evaluated in participants ≥18 to ≤65 years old with pulmonary DS-TB (approximately 43 participants in each regimen). Each agent in the DBOS and PBOS regimens will be administered daily for the full 17 weeks. In addition, approximately 43 participants will receive the global DS-TB treatment standard of care (SOC) of 8 weeks of HRZE followed by 18 weeks of HR (hereafter referred to as '2HRZE/4HR' or 'HRZE regimen') for comparison (Rifafour e-275 tablets Product Label, 2013 for a fixed dose combination form of HRZE or see the product labels for H, R, Z, and E individually that comprise the HRZE regimen recommended as the standard of care for DS-TB treatment in the countries where trial sites are located [eg, Philippines National Tuberculosis Control Program Manual of Procedures 6th Edition, Republic of South Africa Department of Health National Tuberculosis Management Guidelines]). PK profiles of each compound in the DBOS and PBOS regimens will be assessed. The design includes a structured and systematic capture of clinical, safety, microbiologic, and radiographic elements to support an Investigator's assessment and decision to stop treatment after 4 months in the experimental arms, or after 6 months in the SOC arm, and watch for post-treatment disease relapse (traditional endpoint for Phase 3 TB treatment trial); this approach to assessing the stop-treatment-and-watch (STrAW) decision is designed to promote consistency across sites. The dynamics of treatment effect over the 4-month period in the experimental arms and over the 6 months of treatment in the control arm will be closely evaluated in Stage 1 to determine acceptability for advancement to and evaluation of shorter treatment durations in Stage 2.

At the end of Stage 1 (when the last participant of the projected enrollment has at least reached the end of treatment), each of the DBOS and PBOS regimens will be assessed for treatment shortening potential (≤3 months) in DS-TB participants, which will be characterized by the proportion of participants with unfavorable status at Week 17 for DBOS and PBOS and Week 26 for 2HRZE/4HR as well as truncated unfavorable outcome rates at milestone timepoints for each treatment group (see Section 1.3.3 and Section 11.3.1). Because unfavorable status has a composite definition, summaries will also show which individual components of the composite outcome were met. The Stage 1 efficacy and safety results will be reviewed comprehensively to assess treatment shortening potential and benefit/risk. If neither DBOS nor PBOS shows evidence of treatment shortening potential with an acceptable safety profile, the trial will stop, and neither regimen will advance to Stage 2. If only one of the DBOS or PBOS regimens shows evidence of treatment shortening potential with an acceptable safety profile, the trial will be considered for proceeding to Stage 2 with that regimen (referred to hereafter as 'XBOS'). If both DBOS and PBOS show evidence of treatment shortening potential with acceptable safety profiles, the regimen that is considered to proceed to Stage 2 will be the regimen with the more favorable profile overall, including, but not limited to, assessment of safety, tolerability, pharmacokinetics, and alignment with the target regimen profile for a new, affordable, shorter, safer, and simpler TB treatment regimen to treat all TB patients regardless of drug resistance profile.

In Stage 2/Phase 2c, the safety, tolerability, efficacy, and PK of XBOS administered daily across up to 5 treatment durations in the range of 2 to 4 months will be evaluated relative to 2HRZE/4HR in participants aged ≥18 to ≤65 years with pulmonary DS-TB. As with Stage 1, Stage 2 will include the structured and systematic capture of clinical, safety, microbiologic, and radiographic factors to support an Investigator's assessment and decision to stop treatment for a participant at the end of the assigned duration of treatment in the experimental arms and watch for post treatment disease relapse. Stage 2 will also include an evaluation of safety and treatment response dynamics in a cohort of participants with pulmonary RR/MDR-TB to be treated for 4 months with the regimen being advanced. These participants with RR/MDR-TB should have documented fluoroquinolone susceptibility to ensure they have adequate treatment options, including the all oral 9-month regimen or longer individualized regimens as per the recently updated WHO RR/MDR-TB treatment guidelines, in case additional treatment is required following administration of the experimental regimen (WHO, 2022).

1.3.1. Trial Schema

Figure 1 Trial Schema



1.3.2. Overall Design

This is an interventional, multicenter, two-stage, Phase 2b/c, open-label, randomized trial to evaluate the following:

- the treatment shortening potential based on the efficacy and safety of the combination regimens of DBOS and PBOS, administered for 4 months, in participants with pulmonary DS-TB in comparison with the 2HRZE/4HR regimen as assessed by unfavorable outcome status through end of treatment and through 12 months of post-randomization follow-up, as well as sustained sputum culture conversion to negative assessed during the treatment period and at 12 months of post-randomization follow-up (Stage 1)
- the efficacy and safety of varying durations of administration (in the range of 2 to 4 months) of the combination regimen of DBOS or PBOS in participants with pulmonary DS-TB in comparison with the 2HRZE/4HR regimen as assessed by unfavorable outcome status through 12 months of post-randomization follow-up, as well as sustained sputum culture conversion to negative assessed at the end of 12 months post-randomization (Stage 2)
- the safety profile of the combination regimen of DBOS or PBOS, administered for 4 months, in participants with pulmonary RR/MDR-TB compared with the 2HRZE/4HR regimen for participants with DS-TB as well as the efficacy of DBOS or PBOS in this population compared to published reports of outcomes from DR-TB treatment cohorts (Stage 2)

For Stage 1, the treatment shortening potential of the experimental regimens relative to 2HRZE/4HR will be based primarily on unfavorable treatment outcome status. The assessment of treatment outcome status will rely on clinical, radiographic, and microbiological response during and at the end of the 4-month (17 weeks) treatment period compared with 2HRZE/4HR during and at the end of 6 months (26 weeks). In addition to evaluating the status at end of treatment,

unfavorable status based on truncated data at earlier milestone time points will be summarized to create snapshots of unfavorable outcome rates across time for each treatment group. Microbiological response will be assessed by sustained sputum culture conversion (SCC) from growth of Mtb to no growth as defined by 2 successive negative cultures at least 1 week apart. The time required to achieve SCC will also be assessed.

Early data regarding post-treatment relapse occurring in the follow-up period out to 12 months post randomization, particularly among participants enrolled early in the trial, may be available and considered as supportive information in the decision to advance one of the experimental regimens to Stage 2. As two of the compounds included in both regimens – OPC-167832 and sutezolid – are investigational and have only been administered to a limited number of TB patients in completed and on-going clinical trials in DS-TB patients (Wallis et al, 2014; Dawson et al, 2021; Dawson et al, 2023a; Dawson et al, 2023b; Heinrich et al, 2023; www.clinicaltrials.gov, NCT05221502), reviews by the trial's Independent Data Monitoring Committee (IDMC) are planned to occur frequently throughout Stage 1 and 2 (see Section 1.5 for details).

For Stage 2, further assessment of the treatment shortening potential of XBOS will be undertaken by randomizing DS-TB participants across a treatment duration range of 2 to 4 months – specifically 2 months (9 weeks), 2.5 months (11 weeks), 3 months (13 weeks), 3.5 months (15 weeks), and 4 months (17 weeks) for comparison of efficacy and safety with participants randomized to 2HRZE/4HR. For this stage, the primary efficacy assessment will be unfavorable outcome status measured 12 months post-randomization (see Section 11.3.1). A regression model will be used to characterize the relation between regimen duration and unfavorable outcome status assessed at 12 months post-randomization. The regression model will be used to estimate the appropriate duration of the XBOS regimen needed to observe non-inferiority in unfavorable outcomes compared to 2HRZE/4HR in a Phase 3 setting.

The safety profile of XBOS will be assessed in Stage 2 in a cohort of eligible participants with RR/MDR-TB through comparison with the safety profile of 2HRZE/4HR in DS-TB participants. [redacted].

The trial will be conducted at multiple sites in up to 6 countries. Stage 1 will be conducted in approximately 10 to 13 sites, in approximately 3 countries with diverse geographic representation likely in Africa, Asia, and South America. Stage 2 will be conducted in approximately 16 sites in about 6 countries in total.

See Section 1.3.1 for a schematic of the trial design. Trial procedures are summarized in the Schedule of Activities (SoA) flow-charts Table 3 and Table 4 in Section 1.7 below.

1.3.3. Unfavorable Outcome Status

Unfavorable outcome status will serve as the basis for assessment of the primary efficacy endpoint in both Stage 1 and Stage 2. See Section 11.3.1 for the trial definition of unfavorable outcome.

1.3.4. Trial Population

For Stage 1, participants between 18 and 65 (inclusive) years of age of both sexes will be eligible for the trial if they have recently diagnosed, untreated (≤4 days of treatment), microbiologically confirmed, drug susceptible, pulmonary TB. See Section 6.1 and Section 6.2 for details on all inclusion and exclusion criteria. Participants infected with human immunodeficiency virus (HIV) may be enrolled if they are already on permitted antiretroviral treatment (ART) for at least 3 months prior to screening (see Section 7.5.1.1), their CD4+ T-cell count is ≥200 cells/μL, their HIV viral load is <200 copies/mL, and there is no HIV-associated malignancy or clinically significant opportunistic infection (besides TB) present requiring treatment with a prohibited concomitant medication.

For Stage 2, the same eligibility criteria from Stage 1 will apply. Additionally, a small cohort of participants between 18 and 65 years of age (inclusive) of both sexes with untreated (≤4 days of treatment), bacteriologically confirmed, pulmonary RR/MDR-TB (without fluoroquinolone resistance) will be enrolled. HIV-infected participants with DS-TB or RR/MDR-TB may also enroll in Stage 2 with the same criteria as Stage 1 listed above.

1.3.5. Number of Participants

Stage 1 (N = approximately 129)

In Stage 1, the trial will enroll approximately 129 participants. The screening period will last up to 10 days. HIV-infected participants in Peru will not be eligible for the trial due to the requirement for longer TB treatment courses than the standard 6-month HRZE regimen for patients with HIV/TB co-infection as per the Peruvian national TB treatment guidelines (see Section 6.2). The proportion of HIV-infected participants is not expected to exceed 20% of the total Stage 1 sample size, with most (if not all) to be enrolled in South Africa where HIV co-infection is highly prevalent.

Randomization will be stratified by the following two factors for Stage 1:

- Country/HIV status (Peru, Philippines, South Africa and HIV positive, South Africa and HIV negative); and
- TB disease severity measured by extent of disease on screening chest X-ray (CXR) and mycobacterial burden on screening sputum smear and GeneXpert MTB/RIF Ultra (Xpert Ultra), categorized as follows:
    - High severity: >2 lung zones involved on screening CXR or screening sputum smear of 3+ or screening sputum Xpert Ultra cycle threshold <18
    - Low/medium severity: ≤2 lung zones involved on screening CXR and screening sputum smear of ≤2+ and screening sputum Xpert Ultra cycle threshold ≥18.

Eligible participants will be randomized in a ratio of 1:1:1 to one of the following treatment arms:

- Arm 1 (N=43): delamanid + bedaquiline + OPC-167832 + sutezolid (DBOS) for 4 months (17 weeks)
- Arm 2 (N=43): pretomanid + bedaquiline + OPC-167832 + sutezolid (PBOS) for 4 months (17 weeks)

- Arm 3 (N=43): 2HRZE/4HR for 6 months (26 weeks) (8 weeks of HRZE then 18 weeks of HR)

Stage 2 (N = approximately 385)

In Stage 2, the trial will enroll approximately 385 participants. HIV-infected participants in Peru will not be eligible for the trial due to the requirement for longer TB treatment courses than the standard 6-month HRZE regimen for patients with HIV/TB co-infection as per the Peruvian national TB treatment guidelines (see Section 6.2). The proportion of HIV-infected participants is not expected to exceed 20% of the total Stage 2 sample size. Randomization will be stratified by country/HIV status and TB disease severity (high, low/medium) categorized by extent of disease on screening CXR and mycobacterial burden on screening sputum smear and Xpert Ultra. The screening period will last up to 10 days.

Eligible DS-TB participants will be randomized in a ratio of 2:2:2:2:1:1 to one of the following treatment arms:

- Arm 1 (N=70): XBOS for 2 months (9 weeks)
- Arm 2 (N=70): XBOS for 2.5 months (11 weeks)
- Arm 3 (N=70): XBOS for 3 months (13 weeks)
- Arm 4 (N=70): XBOS for 3.5 months (15 weeks)
- Arm 5 (N=35): XBOS for 4 months (17 weeks)
- Arm 6 (N=35): 2HRZE/4HR for 6 months (26 weeks)

Eligible RR/MDR-TB participants will be enrolled into a single-arm cohort:

- XBOS in RR/MDR-TB participants (approximately N=35) for 4 months (17 weeks)

The proportion of participants in the RR/MDR-TB cohort co-infected with HIV is not expected to exceed 20% of the total RR/MDR-TB cohort size.

See Section 11.7 for additional details regarding power and sample size calculations used to derive the sample sizes for the trial.

1.3.6. Dosing (Stages 1 and 2)

The dosing schedule and requirements for the investigational regimens (Regimen 1 & Regimen 2) are presented in Table 1a.

For the dosing schedule and requirements for the SOC regimen (Regimen 3), participants will receive HRZE supplied as HRZE tablets (isoniazid 75 mg, plus rifampicin 150 mg, plus pyrazinamide 400 mg, plus ethambutol 275 mg combination tablets) for 8 weeks. Thereafter, those participants will receive HR supplied as HR tablets (isoniazid 75 mg, plus rifampicin 150 mg combination tablets) for the following 18 weeks. A daily supplement of Vitamin B6 will be taken with HRZE and/or HR, per each country's National TB Treatment Guideline.

The daily dose of HRZE and HR will be based on the participant's weight at screening and during treatment as outlined in Table 1b.

Directly observed therapy (DOT) will be required for adherence monitoring and support in all trial arms in both stages. Specific DOT models utilized, such as home visits by treatment support workers or clinic-based DOT, will be determined by prevailing national guidelines and resources available at each trial site. In addition, video observed therapy (VOT) and medication event reminder monitors, will be used to support adherence and DOT (WHO, 2017a; WHO, 2017b; WHO, 2020). VOT is permitted to substitute for in-person DOT for verification of medication adherence. Doses on weekends and on holidays up to three consecutive days may be self-administered. Details of these measures will be specified in the Trial Operations Manual.

Dosing will be performed on an ambulatory basis. Participants will be instructed to take the component medications of DBOS and PBOS within 1 hour of ingesting food. Participants randomized to 2HRZE/4HR as SOC will be instructed to take the medicines more than 1 hour after ingesting food.

Table 1a Dosing Schedule for Investigational Regimens

Regimen 1*† (Stage 1, Arm 1)	**D** Delamanid	**B** Bedaquiline	**O** OPC-167832	**S** Sutezolid
Dose and Schedule	300 mg once daily (QD) for treatment duration	400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment weeks	30 mg QD for treatment duration	1200 mg QD for treatment duration
Regimen 2*† (Stage 1, Arm 2)	**P** Pretomanid	**B** Bedaquiline	**O** OPC-167832	**S** Sutezolid
Dose and Schedule	200 mg QD for treatment duration	400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment	30 mg QD for treatment duration	1200 mg QD for treatment duration

* Dosing occurs 7 days per week unless specified otherwise.
†See Section 3.3.1.3 (DBOS) and Section 3.3.2.3 (PBOS) for dose selection rationale.

Table 1b Dosing Schedule for SOC Regimen

Intensive Phase						
Weight Band	**Weight Range (kg)Δ**	**Number of FDC Tablets Taken Daily***	**Number of Milligrams of Component Drugs Administered**			
			Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
1	30-37	2	150	300	800	550
2	38-54	3	225	450	1200	825
3	55-70	4	300	600	1600	1100
4	≥71	5	375	750	2000	1375
Continuation Phase						
Weight Band	**Weight Range (kg) Δ**	**Number of FDC Tablets Taken Daily***	**Number of Milligrams of Component Drugs Administered**			
			Isoniazid	**Rifampicin**		
1	30-37	2	150	300		
2	38-54	3	225	450		
3	55-70	4	300	600		
4	≥71	5	375	750		

[Δ] Participant's weight should be rounded down when determining weight band (eg, round 54.9kg to 54kg [Weight Band 2]).
*Fixed dose combination (FDC) of 75mg of isoniazid, 150mg of rifampicin, 400mg of pyrazinamide, and 275mg of ethambutol (HRZE) for the Intensive Phase and 75mg of isoniazid and 150mg of rifampicin (HR) for the Continuation Phase will be utilized.
Note: Dosing occurs 7 days per week unless specified otherwise. WHO treatment guidelines from 2010 and national TB treatment guidelines in countries where trial sites are located serve as the basis for the standard of care dosing schedule (WHO, 2010; Philippines Department of Health, 2020; Republic of South Africa Department of Health, 2014; Peru Ministry of Health, 2013).

1.3.7. Trial Procedures

Safety assessments will include vital signs, ECGs, safety laboratory tests, and collection of solicited and unsolicited AEs, adverse events of special interest (AESIs), and serious AEs (SAEs). Evaluations for cardiac toxicity, hepatotoxicity, hematologic toxicity, and peripheral and optic neuropathy will be conducted throughout the trial to closely monitor for AEs based on the risk profile of the trial drugs (see Section 3.3 and Section 3.4). An IDMC will closely monitor overall trial safety and efficacy in both stages.

Sputum samples will be collected for microbiologic assessment at approximately 15 timepoints per participant from baseline through Week 26 (end of treatment for the 2HRZE/4HR arm) for all treatment arms; additional sputum will be collected for ongoing microbiologic assessment throughout the post-treatment follow up period until 12 months post randomization in order to identify relapses.

1.4. Objectives, Estimands, and Endpoints

All objectives will be assessed in participants with newly diagnosed, pulmonary TB (see inclusion/exclusion criteria, Section 6.1 and Section 6.2). Objectives, estimands, and endpoints are outlined in Table 2. Estimands were constructed based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use's (ICH) E9(R1) addendum on Statistical Principles for Clinical Trials (ICH, 2019) where estimands are defined as "a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. They summarize at a population-level what the outcomes would be in the same patients under different treatment conditions being compared" (ICH, 2019).

Table 2 Trial Objectives, Estimands, and Endpoints

Stage 1 Objectives, Estimands, and Endpoints

Objectives	Estimand	Endpoints
Primary		
Safety		
• To characterize the safety and tolerability of the combination regimens of DBOS and PBOS administered for 4 months compared to 2HRZE/4HR through the end of treatment in participants with pulmonary DS-TB	• In participants receiving at least 1 dose of any trial intervention, the percentage of participants reporting ○ Severe AEs (≥ Grade 3) and/or SAEs through two weeks after the end of treatment in each arm	• Severe AEs (≥ Grade 3) and SAEs through two weeks after the end of treatment (19 weeks for DBOS and PBOS and 28 weeks for 2HRZE/4HR)
Efficacy		
• To assess treatment shortening potential of the combination regimen of DBOS relative to 2HRZE/4HR in participants with pulmonary DS-TB	• In the Per Protocol population (Section 1.8.1), the proportion of participants with unfavorable status at Week 17 for DBOS and Week 26 for 2HRZE/4HR	• Unfavorable outcome status (defined in Section 11.3.1) through end of treatment for each arm
• To assess treatment shortening potential of the combination regimen of PBOS relative to 2HRZE/4HR in participants with pulmonary DS-TB	In the Per Protocol population, the proportion of participants with unfavorable status at Week 17 for PBOS and Week 26 for 2HRZE/4HR	
Secondary		
Safety		
• To assess the safety and tolerability of the combination regimens of DBOS and PBOS administered for 4 months compared to 2HRZE/4HR over 12 months	• In participants receiving at least 1 dose of any trial intervention, the percentage of participants reporting ○ All-cause trial treatment discontinuation in each arm ○ Severe AEs (≥ Grade 3) and/or SAEs through 12 months post randomization	• All-cause permanent trial treatment discontinuation in each arm in all participants • Severe AEs (≥ Grade 3) and SAEs in each arm through the end of the post treatment follow up period (12 months post randomization) in all participants

Objectives	Estimand	Endpoints
• To assess safety and tolerability of the combination regimens of DBOS and PBOS relative to 2HRZE/4HR in participants with pulmonary DS-TB and HIV co-infection	• In participants with HIV co-infection receiving at least 1 dose of trial intervention, the percentage of participants reporting ○ Severe AEs (≥ Grade 3) and/or SAEs in each arm through 12 months post randomization ○ Severe AEs (≥ Grade 3) and/or SAEs through two weeks after the end of treatment in each arm ○ All-cause trial treatment discontinuation in each arm	• Severe AEs (≥ Grade 3) and SAEs in each arm through two weeks after the end of treatment (19 weeks for DBOS and PBOS and 28 weeks for 2HRZE/4HR) in the subset of HIV-infected participants • Severe AEs (≥ Grade 3) and SAEs in each arm through the end of the post treatment follow up period (12 months post randomization) in the subset of HIV-infected participants • All-cause trial treatment discontinuation in each arm in the subset of HIV-infected participants
Efficacy		
• To assess the efficacy of the combination regimens of DBOS and PBOS relative to 2HRZE/4HR in participants with pulmonary DS-TB at the end of post treatment follow-up period (12 months post-randomization)	• In the Per Protocol population, difference in the proportion of participants with unfavorable status in each treatment group at 12 months post-randomization ○ DBOS minus 2HRZE/4HR ○ PBOS minus 2HRZE/4HR	• Unfavorable outcome status at the end of post treatment follow-up period (12 months post-randomization)
• To assess the efficacy of the combination regimens of DBOS and PBOS relative to 2HRZE/4HR in participants with DS-TB and HIV co-infection at the end of treatment and the end of the post treatment follow up period (12 months post-randomization)	• In participants with HIV co-infection in the Per Protocol population, the proportion of participants with unfavorable status in each treatment group at 12 months post-randomization and at the end of treatment.	• Unfavorable outcome status at end of treatment for participants with HIV co-infection • Unfavorable outcome status at end of post treatment follow-up period (12 months post-randomization) for participants with HIV co-infection

Objectives	Estimand	Endpoints
• To investigate the efficacy of the DBOS and PBOS relative to 2HRZE/4HR at 6 months after randomized treatment duration	• In the Per Protocol population, difference in the proportion of participants with unfavorable outcome status at 6 months after the randomized duration of trial treatment o DBOS minus 2HRZE/4HR o PBOS minus 2HRZE/4HR	• Unfavorable outcome status in all arms at 6 months after the randomized duration of trial treatment (ie, 10 months for DBOS and PBOS arms, 12 months for 2HRZE/4HR arm)
• To evaluate and compare the change in Mycobacteria Growth Indicator Tube® (MGIT) culture outcomes in participants receiving the combination regimens of DBOS and PBOS relative to 2HRZE/4HR	• In the Per Protocol population o Hazard ratio for time to sustained sputum culture conversion to negative (DBOS relative to 2HRZE/4HR and PBOS relative to 2HRZE/4HR). o Difference in mean daily rate of change in sputum culture time to detection (TTD) from Baseline to Weeks 4, 8, 9, 13, and 17 (DBOS minus 2HRZE/4HR and PBOS minus 2HRZE/4HR) as calculated from the area under the TTD vs week curve (AUC). o Difference in proportion with sustained sputum culture conversion to negative at each time point through Week 26 post-randomization (DBOS minus 2HRZE/4HR and PBOS minus 2HRZE/4HR)	• Time to sustained sputum culture conversion to negative for Mtb growth in MGIT • Sputum culture time to detection (TTD) curves in MGIT through 4, 8, 9, 13, and 17 weeks of treatment • Sputum culture status for Mtb growth in MGIT at all time points at which sputum culture is assessed during the treatment period.

Objectives	Estimand	Endpoints
• To evaluate and compare the change in solid culture outcomes in participants receiving the combination regimens of DBOS and PBOS relative to 2HRZE/4HR	• In the Per Protocol population o Hazard ratio for time to sustained sputum culture conversion to negative (DBOS relative to 2HRZE/4HR and PBOS relative to 2HRZE/4HR). o Difference in proportion with sustained sputum culture conversion at each time point (DBOS minus 2HRZE/4HR and PBOS minus 2HRZE/4HR)	• Time to sustained sputum culture conversion to negative in solid culture during treatment period. • Sustained sputum culture conversion to negative for Mtb growth in solid culture at all time points at which sputum culture is assessed during treatment period.
• To evaluate emergence of anti-TB drug resistance	• In participants receiving at least 1 dose of trial intervention, the proportion of participants that develop resistance against ≥1 drug during the 12 months post-randomization by treatment group (Note: resistance determination will only be reported for bedaquiline and delamanid among DBOS and PBOS agents as they are the only agents with accepted WHO-recommended critical concentrations). • In participants receiving at least 1 dose of trial intervention, the change in minimum inhibitory concentration (MIC) from baseline to post-baseline for delamanid, pretomanid, bedaquiline, OPC-167832, and sutezolid during the 12 months post randomization by treatment group.	• Resistance result among baseline sputum culture and first culture positive for Mtb at Week 13 or afterwards through 12 months post randomization for delamanid, bedaquiline, isoniazid, rifampicin, pyrazinamide, and/or ethambutol through 12 months post randomization. • MIC values of delamanid, pretomanid, bedaquiline, OPC-167832, and sutezolid performed on baseline sputum culture and first culture positive for Mtb at Week 13 or afterwards through 12 months post randomization.

Objectives	Estimand	Endpoints
PK		
• To evaluate the pharmacokinetics of the individual components of the DBOS and PBOS regimens in all participants with pulmonary DS-TB • To assess the drug-drug interactions (DDI) of antiretroviral medications with the experimental TB regimens in participants with DS-TB and HIV co-infection	• In the PK population: ○ Geometric mean concentration of each analyte at each scheduled time point ○ Geometric coefficient of variation of each analyte concentration at each scheduled time point	• Concentrations of individual anti-TB agents comprising the combination regimens including ○ delamanid and its metabolite DM-6705, bedaquiline and its metabolite M2, OPC-167832, and sutezolid and its active metabolite PNU-101603 for DBOS ○ pretomanid, bedaquiline, and its metabolite M2, OPC—167832, and sutezolid and its active metabolite PNU-101603 for PBOS • For HIV co-infected patients: ○ concentrations of individual antiretroviral medications
Exploratory		
[redacted]		

Objectives	Estimand	Endpoints
[redacted]		

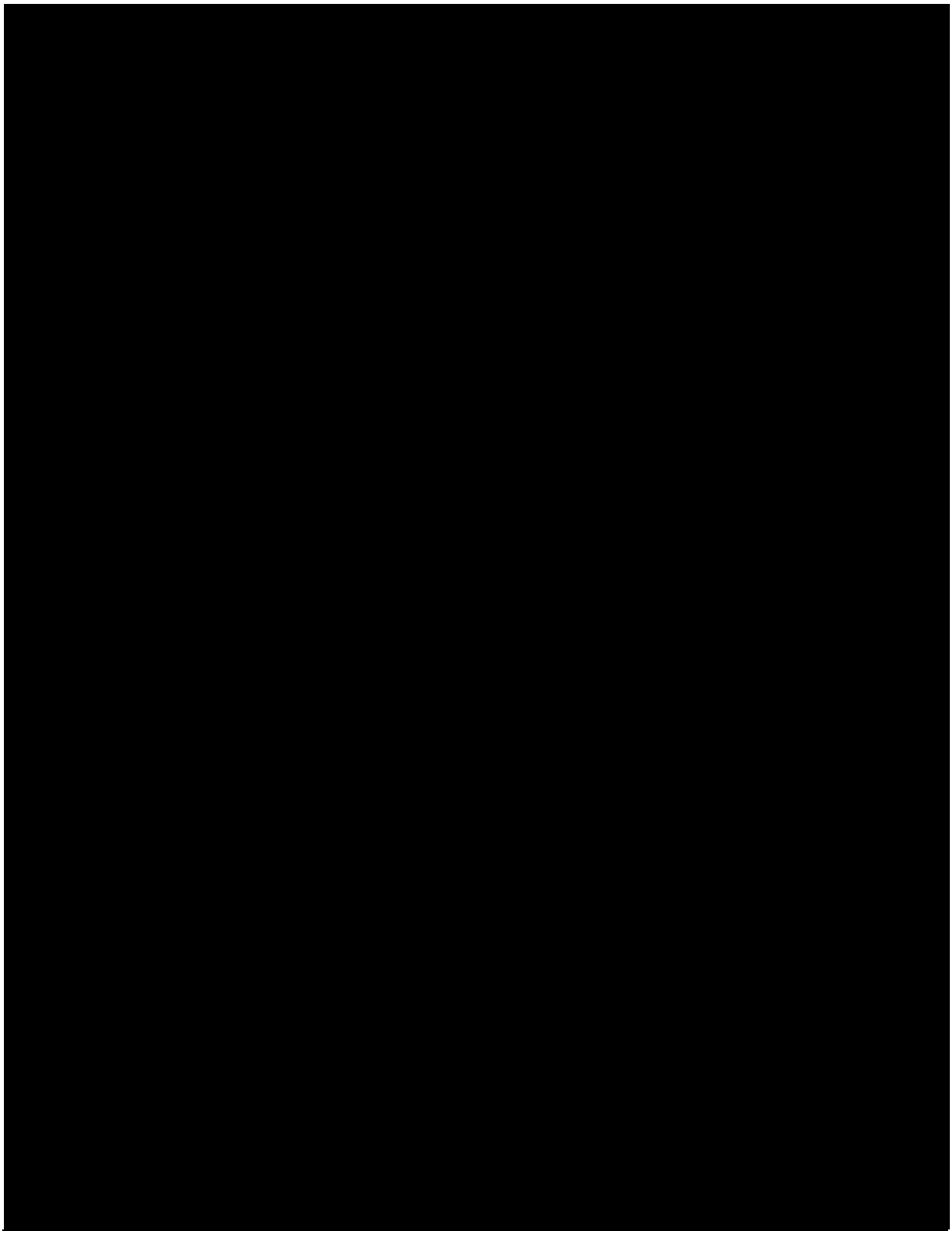
Stage 2 Objectives, Estimands, and Endpoints

Objectives	Estimand	Endpoints
Primary		
Safety		
• To assess the safety and tolerability of XBOS through the end of treatment in DS-TB participants administered XBOS for durations ranging from 2 to 4 months (9 to 17 weeks) compared to 2HRZE/4HR (26 weeks)	• In participants receiving at least 1 dose of trial intervention, the percentage of participants reporting o Severe AEs (≥ Grade 3) and/or SAEs through two weeks after the end of treatment in each arm	• Severe AEs (≥ Grade 3) and SAEs through two weeks after the end of treatment (through 11 to 19 weeks for XBOS arms and through 28 weeks for 2HRZE/4HR arm)
Efficacy		
• To assess the efficacy of the combination regimen of XBOS through 12 months post-randomization in DS-TB participants administered treatment of multiple durations between 2 to 4 months	• In the mITT population, difference in the proportion of participants with unfavorable status at 12 months post-randomization (XBOS minus 2HRZE/4HR), as a function of XBOS treatment duration	• Unfavorable outcome status at end of the post treatment follow-up period (12 months post randomization)
Secondary		
Safety		
• To assess the safety and tolerability of XBOS over 12 months in DS-TB participants administered XBOS for durations ranging from 2 to 4 months (9 to 17 weeks) compared to 2HRZE/4HR (26 weeks)	• In DS-TB participants receiving at least 1 dose of any trial intervention, the percentage of participants reporting o All-cause trial treatment discontinuation in each arm o Severe AEs (≥ Grade 3) and/or SAEs through 12 months post randomization	• All-cause trial treatment discontinuation in each arm in all participants • Severe AEs (≥ Grade 3) and SAEs in each arm through the end of the post treatment follow up period (12 months post randomization) in all DS-TB participants
• To assess safety and tolerability of the combination regimens of XBOS relative to 2HRZE/4HR in participants with pulmonary DS-TB and HIV co-infection	• In DS-TB participants with HIV co-infection receiving at least 1 dose of trial intervention, the percentage of participants reporting o Severe AEs (≥ Grade 3) and/or SAEs through two weeks after the end of treatment in each arm o Severe AEs (≥ Grade 3) and/or SAEs in each arm through 12 months post randomization o All-cause trial treatment discontinuation in each arm	• Severe AEs (≥ Grade 3) and SAEs in each arm through two weeks after the end of the treatment in the subset of HIV-infected participants • Severe AEs (≥ Grade 3) and SAEs in each arm through the end of the post treatment follow up period (12 months post randomization) in the subset of HIV-infected participants • All-cause trial treatment discontinuation in each arm in the subset of HIV-infected participants

Objectives	Estimand	Endpoints
Secondary (continued)		
• To assess safety of XBOS administered for 4 months in RR/MDR-TB participants compared with relevant national program data and historical reports	• In RR/MDR-TB participants receiving at least 1 dose of trial intervention, the percentage of participants reporting: o Severe AEs (≥ Grade 3) and/or SAEs through two weeks after the end of treatment o Severe AEs (≥ Grade 3) and/or SAEs through the end of post treatment follow up at 12 months o All-cause trial treatment discontinuation	• Severe AEs (≥ Grade 3) and SAEs in RR/MDR-TB arm through two weeks after the end of the treatment (19 weeks) • Severe AEs (≥ Grade 3) and SAEs in RR/MDR-TB arm through the end of the post treatment follow up period (12 months post randomization) • All-cause trial treatment discontinuation in RR/MDR-TB arm
Efficacy		
• To assess the efficacy of the combination regimen XBOS in participants with pulmonary DS-TB at the end of treatment	• In the mITT population, difference in the proportion of participants with unfavorable outcome status at the end of treatment (XBOS minus 2HRZE/4HR), as a function of XBOS treatment duration.	• Unfavorable outcome status at the end of treatment in all arms
• To assess the efficacy of the combination regimen of XBOS in participants with DS-TB and HIV co-infection at the end of treatment and 12 months post-randomization	• In participants with HIV co-infection in the mITT population, the proportion unfavorable status in each treatment group	• Unfavorable outcome status amongst participants with DS-TB and HIV co-infection (end of treatment and 12 months post-randomization)
• To investigate the efficacy of the XBOS combination regimen at the same time point (6 months) after randomized treatment duration	• In the mITT population, difference in the proportion of participants with unfavorable outcome status at 6 months after the randomized duration of trial treatment (XBOS minus 2HRZE/4HR)	• Unfavorable outcome status in all arms at 6 months after the randomized duration of trial treatment

Secondary (continued)		
• To evaluate and compare the change in Mycobacteria Growth Indicator Tube® (MGIT) culture outcomes in participants receiving the combination regimen of XBOS relative to 2HRZE/4HR	• In the mITT population o Hazard ratio for time to sustained sputum culture conversion to negative (pooled XBOS arms relative to 2HRZE/4HR). o Difference in mean daily rate of change in sputum culture time to detection (TTD) in MGIT from Baseline to Weeks 4, 8, 9, 11, 13, 15, and 17 (pooled XBOS arms minus 2HRZE/4HR) as calculated from the area under the TTD vs week curve (AUC). o Difference in proportion with sustained sputum culture conversion to negative at Week 8 and EOT (pooled XBOS arms minus 2HRZE/4HR). o Difference in proportion with sustained sputum culture conversion to negative at each time point (XBOS minus 2HRZE/4HR as a function of XBOS treatment duration).	• Time to sustained sputum culture conversion to negative for Mtb growth in MGIT • Sputum culture MGIT TTD curves through 4, 8, 9, 11, 13, 15, and 17 weeks of treatment • Sustained sputum culture conversion to negative for Mtb growth in MGIT at all time points at which sputum culture is assessed during treatment period
• To evaluate and compare the change in solid culture outcomes in participants receiving the combination regimen of XBOS relative to 2HRZE/4HR	• In the mITT population o Hazard ratio for time to sustained sputum culture conversion to negative (pooled XBOS arms relative to 2HRZE/4HR). o Difference in proportion with sustained sputum culture conversion to negative at Week 8 and EOT (pooled XBOS arms minus 2HRZE/4HR). o Difference in proportion with sustained sputum culture conversion to negative at each time point (pooled XBOS arms minus 2HRZE/4HR)	• Time to sustained sputum culture conversion to negative in solid culture during treatment period. • Sustained sputum culture conversion to negative for Mtb growth in solid culture at all time points at which sputum culture is assessed during treatment period.
• To evaluate emergence of anti-TB drug resistance	• In participants receiving at least 1 dose of trial intervention, the proportion of participants that develop resistance against ≥1 drug	• Resistance result among baseline sputum culture and first culture positive for Mtb at Week 9 or afterwards for Arm 1, Week 11 or afterwards for Arm 2, and Week 13

	during the 12 months post randomization by treatment group (Note: resistance determination will only be reported for bedaquiline and delamanid among DBOS and PBOS agents as they are the only agents with accepted WHO-recommended critical concentrations). • In participants receiving at least 1 dose of trial intervention, the change in MIC from baseline to post-baseline for delamanid, pretomanid, bedaquiline, OPC-167832, and sutezolid during the 12 months post randomization by treatment group.	or afterwards for Arms 3 to 6 and the RR/MDR-TB cohort through 12 months post randomization for delamanid, bedaquiline, isoniazid, rifampicin, pyrazinamide, and/or ethambutol • MIC values of delamanid, pretomanid, bedaquiline, OPC-167832, and sutezolid performed on baseline sputum culture and first culture positive for Mtb at Week 9 or afterwards for Arm 1, Week 11 or afterwards for Arm 2, and Week 13 or afterwards for Arms 3 to 6 and the RR/MDR-TB cohort through 12 months post randomization.
PK		
• To evaluate the PK of the individual components in the XBOS regimen in all participants with pulmonary DS-TB and RR/MDR-TB • To assess the drug-drug interactions (DDI) of antiretroviral medications with the experimental TB regimens in participants with DS-TB and HIV co-infection	• In the PK population: o Geometric mean concentration of each analyte at each scheduled time point o Geometric coefficient of variation of each analyte concentration at each scheduled time point	• For DS-TB and RR/MDR-TB participants, concentrations of individual anti-TB agents comprising the XBOS regimen, including o delamanid and its metabolite DM-6705 or pretomanid, bedaquiline and its metabolite M2, OPC-167832, and sutezolid and its active metabolite PNU-101603 • For HIV co-infected patients: o concentrations of individual antiretroviral medications
Exploratory		
[redacted]		



1.5. Independent Data Monitoring Committee (IDMC)

An IDMC will be established to oversee the safety of this trial and monitor for futility (see Section 11.6). The IDMC will operate according to a charter. The IDMC structure, participants, and other details will be provided in the charter. The charter will be available prior to trial start. As two of the compounds included in both regimens – OPC-167832 and sutezolid – are investigational and have only been administered for up to 2 weeks in completed clinical trials in DS-TB patients, regular reviews by the trial's IDMC are planned. IDMC meetings are planned to occur during Stage 1 approximately after one-third, two-thirds, and all of the 129 participants are enrolled (roughly quarterly), after the last Stage 1 participant has completed treatment, and approximately every 3 to 4 months in Stage 2 with ad hoc meetings as needed.

The IDMC will review the unmasked comprehensive safety data, available microbiology and clinical data, and, if available, PK data, during regularly scheduled safety review meetings and specified interim analyses for safety assessments. The IDMC may request additional information, or recommend a pause in recruitment and trial treatment, while safety data are being evaluated. All procedures associated with these reviews, including objectives, data handling, elements included for review, and recommendations will be documented. The IDMC will make a formal recommendation to the Sponsor on the continued enrolment into the trial after each safety review.

Additionally, the IDMC will convene on an ad hoc basis as needed for emerging safety findings occurring in between scheduled meetings including scenarios such as more than one participant having trial drug administration paused for reason related to trial drug.

The recommendation of the IDMC, along with the Sponsor's decision, will be communicated to the Investigators, the IRBs/IECs, and the national regulatory authorities as required. The Sponsor or its designee agrees to abide to any directives issued by the national regulatory authorities or the IRBs/IECs for the trial sites under the jurisdiction of that regulatory authority or IRB/IEC.

1.6. Stop Treatment and Watch (STrAW) Concilium

The STrAW Concilium will be established for the trial to provide expert clinical consultation to Investigators on challenging clinical scenarios, including all participants where the Investigator wants to permanently stop one or more trial medications, continue trial treatment past the assigned duration, or restart TB treatment after the completion of trial treatment (see Section 8.3.2 and Section 9.5.4).

The STrAW Concilium will be composed of independent experts in TB clinical management with an understanding of mycobacteriology and experience in the conduct of TB clinical trials. The Concilium will operate according to a charter detailing its structure, participants, and procedures. Concilium members will be partially blinded to study regimen assignment (see Section 7.3.2).

1.7. Schedule of Activities (SoA)

Table 3 Schedule of Assessments – Stage 1

Period	Pre-Treatment Period		Treatment and Follow-up Period																						
Visit	SCR 1	BL 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	PTR N/A	ET N/A
	Day		Week** (±4 days)															Month (±7 days)							
Day/Week/Month	−10 to −2	1[a]	1	2	4	6	8	9	11	13	15	17	19	21	23	26	28[b]	7	8	9	10	11	12	N/A	N/A
DBOS or PBOS Treatment (Arms 1 and 2)[c]		X	X	X	X	X	X	X	X	X	X	X													
2HRZE/4HR Treatment (Arm 3)[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Eligibility and Randomization																									
Informed consent	X																								
Inclusion/Exclusion assessment	X	X																							
Demographics	X																								
Medical history	X																								
Randomization		X																							
Clinical Evaluation																									
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X	X[j]	X		X	X	X	X	X	X	X	X
TB Signs & Symptoms Questionnaire[e]		X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X	X
Review of systems and physical exam[f]	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X	X
Visual assessment[g]	X	X			X			X		X		X		X		X		X					X		X
Peripheral neuropathy		X			X			X		X		X		X		X		X					X		X

Period	Pre-Treatment Period		Treatment and Follow-up Period																							
Visit	SCR 1	BL 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	PTR N/A	ET N/A
	Day		Week** (±4 days)															Month (±7 days)							
Day/Week/Month	−10 to −2	1[a]	1	2	4	6	8	9	11	13	15	17	19	21	23	26	28[b]	7	8	9	10	11	12	N/A	N/A
screen[h]																									
Functional status assessment[i]	X							X			X			X									X	X	X
Mid-upper arm circumference		X						X				X				X							X	X	X
Treatment																									
IMP dispensing[j]		X	X	X	X	X	X	X	X	X	X	X[j]	X[j]	X[j]	X[j]										
IMP adherence assessment[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing																									
Complete blood count and reticulocyte count	X			X	X	X		X		X		X		X		X							X	X	X
Biochemistry[l]	X		X	X	X	X	X	X	X	X		X		X		X							X	X	X
Creatine kinase	X				X			X		X		X		X											X
Hemoglobin A1c[m]	X															X[m]							X[m]		
HIV test[n], Hep B sAg, anti-Hep C Ab	X																								
CD4 count and viral load for HIV+[o]	X									X[o]						X[o]				X[o]			X[o]	X[o]	X[o]
C-reactive protein (CRP)	X			X	X	X		X		X		X		X		X							X	X	X

Period	Pre-Treatment Period		Treatment and Follow-up Period																						
Visit	SCR 1	BL 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	PTR N/A	ET N/A
	Day		Week** (±4 days)															Month (±7 days)							
Day/Week/Month	−10 to −2	1[a]	1	2	4	6	8	9	11	13	15	17	19	21	23	26	28[b]	7	8	9	10	11	12	N/A	N/A
PK[p]		X	X	X	X	X		X	X	X	X	X	X	X	X	X				X			X		X
Pregnancy test[q]	X	X			X		X		X		X		X		X	X		X	X	X	X	X	X		X
Pharmacogenomics sample[r]		X																							
Paxgene tube for transcriptomics		X	X	X	X	X		X		X		X		X		X				X			X	X	X
[redacted]																									
Urine dipstick and microscopy	X																								
Urine drug screen	X																								
Urine INH[s]					X			X		X		X		X		X									
Respiratory sample for SARS-CoV-2 PCR[t]	X																							X	X
Sputum Testing																									
Sputum collection[u]	X	XXX	XXX	XXX	XXX	XXX	XX	XXX	XX	XXX	XX	XXX	XX	XXX	XX	XXX	XX	XX	XX	XXX	XX	XX	XXX	XXX	XXX
Smear microscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X	X	X	X	X	X	X
Rapid molecular test for INH & RIF resistance detection	X																								
Culture (MGIT and solid)[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X	X	X	X	X	X	X

Period	Pre-Treatment Period		Treatment and Follow-up Period																						
Visit	SCR 1	BL 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	PTR N/A	ET N/A
	Day		Week** (±4 days)															Month (±7 days)							
Day/Week/Month	−10 to −2	1[a]	1	2	4	6	8	9	11	13	15	17	19	21	23	26	28[b]	7	8	9	10	11	12	N/A	N/A
[redacted]																									
Drug susceptibility[w]		X																						X	
Mtb strain Genotyping[x]		X																							
[redacted]																									
Other Procedures																									
Standard 12-lead ECG	X			X	X			X		X		X		X		X							X		X
PA CXR	X				X			X				X				X							X	X	X[y]
Spirometry[z]		X						X				X				X							X	X	X

** Week number represents the last day of the respective week (eg, Week 1 assessment = Day 8; Week 2 assessment = Day 15, etc.)
SCR=screening; BL=baseline; PTR=poor treatment response; ET=early termination; For additional abbreviations, see List of Abbreviations

a Day 1 is defined by the first day a participant takes trial treatment. Other baseline visit procedures may be done before the first day of trial treatment administration.
b The Week 28 visit (Visit 17) will be performed only for participants randomized to Arm 3.
c Dosing will be daily through the end of treatment except bedaquiline, which is dosed daily for 14 days and then given thrice weekly.
d The following vital signs should be measured at every visit: temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight. Height will be measured only at screening. Body mass index (BMI) will be calculated at every visit that weight is measured using the height measured at the screening visit. Oxygen saturation, blood pressure, heart rate, and respiratory rate should be measured in the sitting or supine position after the participant has rested for ≥2 minutes. Vital signs do not need to be recorded at Week 19, Week 23, and Week 28 visits except for weight at Week 19 and Week 23 visits for participants in Arm 3 (2HRZE/4HR) to inform any weight-based dose adjustment indicated.
e TB Signs & Symptoms Questionnaire will include a structured questionnaire and cough status assessment.

f At the initial screening visit, a complete physical examination should be performed. At all other visits, a targeted physical examination should be performed focused on participant-driven issues eg, the Investigator inquires if the participant has any complaints, pains, or disturbances and this would lead to further evaluation of the problematic area. At a minimum, an assessment of general appearance and a cardiopulmonary examination should be performed.

g Visual assessments will consist of visual acuity and color vision screenings throughout the trial and a fundoscopic exam by the Investigator or delegate at the initial screening visit (see Section 9.1.9).

h Peripheral neuropathy screening will be conducted using the Brief Peripheral Neuropathy Screening (BPNS) tool.

i The Karnofsky Performance Status scale will be used to assess functional status.

j Only Arm 3 (2HRZE/4HR participants) will receive IMP treatment from Weeks 18-26. Weight should be measured at Week 19 and Week 23 visits for Arm 3 participants to inform any weight-based dose adjustment required (no other vital signs are required at Week 19 or Week 23 visits).

k Adherence assessments can include collection of video DOT and medication event reminder system data in addition to pill counts and treatment supporter adherence logs.

l Biochemistry tests include creatinine, blood urea nitrogen, estimated glomerular filtration rate, potassium, sodium, chloride, serum bicarbonate, calcium, magnesium, ALT, AST, total and direct bilirubin, alkaline phosphatase, total protein, albumin, and lactate dehydrogenase.

m Hemoglobin A1c should be repeated at Week 26 and Month 12 if a participant's hemoglobin A1c was ≥6.5% at screening.

n HIV testing should be done during screening if: a) the participant's HIV status is unknown, b) the participant reports being HIV negative or c) the participant reports being HIV-infected but cannot provide written documentation of their HIV status at screening, such as documentation in a medical record or book. Participants found to be HIV-negative at screening should be retested during the trial according to their country's national HIV testing guidelines.

o CD4 count and HIV viral load will only be performed for HIV-infected participants.

p PK samples will be taken on the following schedule for participants randomized to Arms 1 and 2 (PK will not be assessed for Arm 3 [2HRZE/4HR]): Baseline visit (to serve as predose sample), Week 1 (predose and 2-6 h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6 h postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), and Week 17 (predose). PK samples will be collected at the following post-treatment study visits for testing of bedaquiline and its metabolite only: Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12. 18 PK samples will be collected per participant in total. Participants still on trial treatment undergoing an Early Termination visit should have sample(s) for PK collected. Ideally, predose and 2–6-hour postdose samples should be collected, but a single random sample is acceptable.

q For women of childbearing potential only, serum β-hCG will be collected at the first screening visit. Point-of-care urine pregnancy testing will be done at the baseline visit. After randomization, either point-of-care urine pregnancy testing or serum β-hCG testing will be performed approximately every 3-4 weeks throughout the trial.

r Pharmacogenomic sample collection will only be performed for participants that provide specific consent for it.

s Urine isoniazid (INH) testing will be performed only for participants randomized to Arm 3 (2HRZE/4HR) in Stage 1.

t PCR testing for SARS-CoV-2 will be conducted on a nasopharyngeal or oropharyngeal sample at the initial screening visit for eligibility determination. It will also be performed at visits conducted for suspected poor treatment response and early termination unless reason for early termination is pregnancy or withdrawal of consent. SARS-CoV-2 PCR can also be performed at any time during the trial that an Investigator suspects new and unexplained symptoms of possible COVID-19 infection or if the participant is a contact of a confirmed COVID-19 case.

u One spot sputum will be collected at the initial screening visit. At baseline visit, three spot sputum specimens will be collected before the first dose of study treatment is administered. From Week 1 onwards, up to three sputum specimens will be collected, including a first-morning sputum and two spot sputum specimens. At visits where sputum for [redacted]. See Section 9.3 for further details. Note: The number of these X's reflects the number of sputum specimens to be collected at respective timepoints.

v Mtb culture isolates will be stored for all positive cultures for DST/MIC, genotyping, and any repeat/[redacted] that may be required.

w DST will be performed on the baseline visit or Week 1 sputum culture depending on suitability of culture growth for DST performance. DST will also be performed on the first culture positive for Mtb at Week 13 or afterwards in all arms. DST may be performed on additional cultures positive for Mtb if deemed pertinent by the Sponsor.

x Genotyping will be performed on a Mtb-positive culture from baseline visit or Week 1 depending on suitability of culture growth as well as the first of any subsequent Mtb-positive culture occurring from the end of treatment study visit through the end of the post-treatment follow-up period for suspected relapse cases (the post-treatment follow-up period begins at the Week 17 visit for Arms 1 and 2 and at the Week 26 visit for Arm 3). In addition, the Sponsor may perform genotyping at other time points as needed.

y A CXR should be performed at the early termination visit for any participant withdrawn due to suspected or confirmed TB treatment failure and/or disease relapse.

z In addition to spirometry assessments conducted at baseline visit, Week 9, Week 17, Week 26, and Month 12 visits, spirometry should be attempted to be performed at poor treatment response visit as well as early termination visit for any participant withdrawn due to suspected or confirmed TB treatment failure and/or disease relapse. Recommended infection prevention and control measures for conducting spirometry are detailed in the Trial Operations Manual. If a site is unable to implement sufficient infection prevention and control measures to ensure the safe conduct of spirometry the Sponsor can designate the site as a non-spirometry site and omitted spirometry assessments at these sites will not be considered protocol deviations.

Table 4 Schedule of Assessments – Stage 2

Period	Pre-Treatment Period		Treatment and Follow-up Period																					
	SCR	BL																						
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	PTR	ET
	Day		Week** (±4 days)															Month (±7 days)						N/A	N/A
Day/Week/Month	−10 to −2	1[a]	1	2	4	6	8	9[b]	11[b]	13[b]	15[b]	17[b]	19	21	23	26	28[c]	7	8	9	10	11	12	N/A	N/A
XBOS Treatment (Arms 1-5)[b]		X	X	X	X	X	X	Treatment duration is dependent on arm. See footnote b																	
2HRZE/4HR Treatment (Arm 6)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
XBOS Treatment (RR/MDR-TB Arm)		X	X	X	X	X	X	X	X	X	X	X													
Eligibility and Randomization																									
Informed consent	X																								
Inclusion/Exclusion assessment	X	X																							
Demographics	X																								
Medical history	X																								
Randomization		X																							
Clinical Evaluation																									
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X	X[j]	X		X	X	X	X	X	X	X	X
TB Signs & Symptoms Questionnaire[e]		X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X	X
Review of systems and physical exam[f]	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X	X
Visual assessment[g]	X	X			X			X		X		X		X		X		X					X		X
Peripheral neuropathy screen[h]		X			X			X		X		X		X		X		X					X		X
Functional status assessment[i]	X							X			X			X									X	X	X

Period	Pre-Treatment Period		Treatment and Follow-up Period																					
	SCR	BL																						
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	PTR	ET
	Day		Week** (±4 days)															Month (±7 days)						N/A	N/A
Day/Week/Month	−10 to −2	1[a]	1	2	4	6	8	9[b]	11[b]	13[b]	15[b]	17[b]	19	21	23	26	28[c]	7	8	9	10	11	12	N/A	N/A
Mid-upper arm circumference		X						X				X				X							X	X	X
Treatment																									
IMP dispensing[j]		X	X	X	X	X	X	X	X	X	X	X[j]	X[j]	X[j]	X[j]										
IMP adherence assessment[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing																									
Complete blood count and reticulocyte count	X			X	X	X		X	X[l]	X	X[l]	X		X		X							X		X
Biochemistry[m]	X		X	X	X	X	X	X	X	X		X		X		X							X		X
Creatine kinase	X				X			X		X		X		X											X
Hemoglobin A1c[n]	X															X[n]							X[n]		
HIV test[o], Hep B sAg, anti-Hep C Ab	X																								
CD4 count and viral load for HIV+[p]	X									X[p]						X[p]				X[p]			X[p]	X[p]	X[p]
C-reactive protein (CRP)	X			X	X	X		X	X[l]	X	X[l]	X		X		X							X	X	X
PK[q]		X	X	X	X	X		X	X	X	X	X	X	X	X	X				X			X		X
Pregnancy test[r]	X	X			X		X		X		X		X		X	X		X	X	X	X	X	X		X
Pharmacogenomics sample[s]		X																							
Paxgene tube for transcriptomics		X	X	X	X	X		X	X[t]	X	X[t]	X		X		X				X			X	X	X

Period	Pre-Treatment Period		Treatment and Follow-up Period																					
	SCR	BL																						
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	PTR	ET
	Day		Week** (±4 days)															Month (±7 days)						N/A	N/A
Day/Week/Month	−10 to −2	1[a]	1	2	4	6	8	9[b]	11[b]	13[b]	15[b]	17[b]	19	21	23	26	28[c]	7	8	9	10	11	12	N/A	N/A
[redacted]																									
Urine dipstick and microscopy	X																								
Urine INH[u]					X			X		X		X		X		X									
Urine drug screen	X																								
Respiratory sample for SARS-CoV-2 PCR[v]	X																							X	X
Sputum Testing																									
Sputum collection[w]	X	XXX	XXX	XXX	XXX	XX X	XX	XX X	XXX	XXX	XXX	XXX	XX	XXX	XX	XXX	XX	XX	XX	XXX	XX	XX	XXX	XXX	XXX
Smear microscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X	X	X	X	X	X	X	X
Rapid molecular test for INH & RIF resistance detection	X																								
Rapid molecular test for FQ resistance detection only for RR/MDR-TB cohort	X[x]																								
Culture (MGIT and solid)[y]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X	X	X	X	X	X	X	X
[redacted]																									
Drug susceptibility[z]		X																							

Period	Pre-Treatment Period		Treatment and Follow-up Period																					
	SCR	BL																						
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	PTR	ET
	Day		Week** (±4 days)															Month (±7 days)						N/A	N/A
Day/Week/Month	−10 to −2	1[a]	1	2	4	6	8	9[b]	11[b]	13[b]	15[b]	17[b]	19	21	23	26	28[c]	7	8	9	10	11	12	N/A	N/A
MTB strain genotyping[aa]		X																							
[redacted]																									
Other Procedures																									
Standard 12-lead ECG	X			X	X			X	X[1]	X	X[1]	X		X		X								X	X
PA CXR	X				X			X				X				X							X	X	X[bb]
Spirometry[cc]		X						X				X				X							X	X	X
[redacted]																									

** Week number represents the last day of the respective week (eg, Week 1 assessment = Day 8; Week 2 assessment = Day 15, etc.)
SCR=screening; BL=baseline; PTR=poor treatment response; ET=early termination; For additional abbreviations, see List of Abbreviations

a Day 1 is defined by the first day a participant takes trial treatment. Other baseline visit procedures may be done before the first day of trial treatment administration.

b Dosing will be daily through the end of treatment except bedaquiline, which is dosed daily for 14 days and then given thrice weekly.
Arm 1: XBOS for 2 months (9 weeks); Arm 2: XBOS for 2.5 months (11 weeks); Arm 3: XBOS for 3 months (13 weeks); Arm 4: XBOS for 3.5 months (15 weeks); Arm 5: XBOS for 4 months (17 weeks); Arm 6: 2HRZE/4HR regimen for 6 months (26 weeks); RR/MDR-TB cohort: XBOS for 4 months (17 weeks). Adherence assessments can include collection of video DOT and medication event reminder system data in addition to pill counts and treatment supporter adherence logs.

c The Week 28 visit (Visit 17) will be performed only for participants randomized to Arm 6.

d The following vital signs should be measured at every visit: temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight. Height will be measured only at screening. BMI will be calculated at every visit that weight is measured using the height measured at the screening visit. Blood pressure, heart rate, and respiratory rate should be measured in the sitting or supine position after the participant has rested for ≥2 minutes. Vital signs do not need to be recorded at Week 19, Week 23, and Week 28 visits except for weight measurement at Week 19 and Week 23 visits for participants in Arm 6 (2HRZE/4HR) to inform any adjustment in weight-based dosing required.

e TB Signs & Symptoms Questionnaire will include a structured questionnaire and cough status assessment. Additionally, cough monitoring data will be collected for participants that provide specific consent to participate in that assessment.

f At the initial screening visit a complete physical examination should be performed. At all other visits, a targeted physical examination should be performed focused on participant-driven issues eg, the Investigator enquires if the participant has any complaints, pains, or disturbances and this would lead to further evaluation of the problematic area. At a minimum, an assessment of general appearance and a cardiopulmonary examination should be performed.

g Visual assessments will consist of visual acuity and color vision screenings throughout the trial and a fundoscopic exam by the Investigator or delegate at the initial screening visit (see Section 9.1.9).

h Peripheral neuropathy screening will be conducted using the Brief Peripheral Neuropathy Screening (BPNS) tool.

i The Karnofsky Performance Status scale will be used to assess functional status.

j Only Arm 6 (2HRZE/4HR participants) will receive IMP treatment from Weeks 18-26. Participants in investigational treatment Arms 1-5 will have IMP dispensed according to their treatment arm (see footnote 'b'). Weight should be measured at Week 19 and Week 23 visits for Arm 6 participants to inform any weight-based dose adjustment required (no other vital signs are required at Week 19 and Week 23).

k Adherence assessments can include collection of video DOT and medication event reminder system data in addition to pill counts and treatment supporter adherence logs.

l End-of-treatment assessments will be performed only at Week 11 for Arm 2 and Week 15 for Arm 4

m Biochemistry tests include creatinine, blood urea nitrogen, estimated glomerular filtration rate, potassium, sodium, chloride, serum bicarbonate, calcium, magnesium, ALT, AST, total and direct bilirubin, alkaline phosphatase, total protein, albumin, and lactate dehydrogenase.

n Hemoglobin A1c should be repeated at Week 26 and Month 12 if a participant's hemoglobin A1c was ≥6.5% at Screening.

o HIV test should be done during screening if: a) the participant's HIV status is unknown, b) the participant reports being HIV negative or c) the participant reports being HIV-infected but cannot provide written documentation of their HIV status at screening, such as documentation in a medical record or book. Participants found to be HIV-negative at screening should be retested during the course of the trial according to their country's national HIV testing guidelines.

p CD4 count and HIV viral load will only be performed for HIV-infected participants.

q PK samples will be taken on the following schedule for participants randomized to Arms 1 to 5 and RR/MDR-TB cohort (PK will not be assessed for Arm 6 [2HRZE/4HR]): Baseline visit (to serve as predose sample), Week 1 (predose and 2-6h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6h postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), and Week 17 (predose). PK samples will be collected at the following post-treatment study visits for testing of bedaquiline and its metabolite only: Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12. 18 PK samples will be collected per participant in total. Participants still on trial treatment undergoing an Early Termination visit should have sample(s) for PK collected. Ideally, predose and 2–6-hour postdose samples should be collected, but a single random sample is acceptable.

r For women of childbearing potential only, serum β-hCG will be collected at the first screening visit. Point-of-care urine pregnancy testing will be done at the baseline visit. After randomization, either point-of-care urine pregnancy testing or serum β-hCG testing will be performed approximately every 3-4 weeks throughout the trial.

s Pharmacogenomic sample collection will only be performed for participants that provide specific consent for it.

t [redacted]

u Urine INH testing will be performed only for participants randomized to Arm 6 (2HRZE/4HR) in Stage 2.

v PCR testing for SARS-CoV2 will be conducted on a nasopharyngeal or oropharyngeal sample at the initial screening visit for eligibility determination. It will also be performed at visits conducted for suspected poor treatment response and early termination unless reason for early termination is pregnancy or withdrawal of consent. SARS-CoV-2 PCR can also be performed at any time during the trial that an Investigator suspects new and unexplained symptoms of possible COVID-19 infection or if the participant is a contact of a confirmed COVID-19 case.

w One spot sputum will be collected at the initial screening visit. At baseline visit, three spot sputum specimens will be collected before the first dose of study treatment is administered. From Week 1 onwards, up to three sputum specimens will be collected, including a first-morning sputum and two spot sputum specimens. At visits where sputum for [redacted]. See Section 9.3 for further details. Note: The number of these X's reflects the number of sputum specimens to be collected at respective timepoints.

x A rapid molecular test(s) for detecting fluoroquinolone resistance (eg, HAIN LPA second line, Xpert MTB/XDR) will be conducted for participants being evaluated for the RR/MDR-TB cohort in Stage 2.

y [redacted].

z DST will be performed on the baseline visit or Week 1 sputum culture depending on suitability of culture growth for DST performance. DST will also be performed on the first culture positive for Mtb at Week 9 or afterwards for Arm 1, Week 11 or afterwards for Arm 2, and Week 13 or afterwards for Arms 3 to 6 and the RR/MDR-TB cohort. DST may be performed on additional cultures positive for Mtb if deemed pertinent by the Sponsor.

aa Genotyping will be performed on a Mtb-positive culture from baseline visit or Week 1 depending on suitability of culture growth as well as the first of any subsequent Mtb-positive culture occurring from the end of treatment study visit through the end of the post-treatment follow-up period for suspected relapse cases (post-treatment follow-up period starts at the respective end-of-treatment visit for each arm). In addition, the Sponsor may perform genotyping at other time points as needed.

bb A CXR should be performed at the early termination visit for any participant withdrawn due to suspected or confirmed TB treatment failure and/or disease relapse.

cc In addition to spirometry assessments conducted at baseline visit, Week 9, Week 17, Week 26, and Month 12 visits, spirometry should be attempted to be performed at the poor treatment response visit as well as early termination visit for any participant withdrawn due to suspected or confirmed TB treatment failure and/or disease relapse. Recommended infection prevention and control measures for conducting spirometry are detailed in the Trial Operations Manual. If a site is unable to implement sufficient infection prevention and control measures to ensure the safe conduct of spirometry, omitted spirometry assessments will not be considered protocol deviations.

dd [redacted]

1.8. Statistical Considerations

This section contains a brief summary of the statistical analyses to support the primary and secondary objectives of this trial.

1.8.1. Populations for Analysis

See Section 11.1 for definitions of the populations for purposes of the statistical analyses.

1.8.2. Statistical Hypotheses

See Section 11.2 for the primary hypotheses for Stage 1 and Stage 2.

1.8.3. Primary and Key Secondary Endpoints

See Section 1.4 and Section 11.3 for the primary and key secondary trial endpoints.

1.8.4. Statistical Methods

See Section 11.4 for a summary of the statistical methods planned for Stage 1 and Stage 2.

1.8.5. Interim Analyses

An interim analysis will be performed after all Stage 1 participants have reached the end of treatment to assess the treatment shortening potential of DBOS and PBOS.

Regular monitoring for futility by the IDMC based on the 12-months post-randomization unfavorable outcome rate endpoint will be implemented in both Stage 1 and Stage 2, after at least 20 participants have been enrolled in each group.

See Section 11.6 for details.

1.8.6. Sample Size Justification

Stage 1

In Stage 1, approximately 43 participants per arm will be enrolled in a 1:1:1 randomization ratio to the treatment groups described in Figure 1. The operating characteristics of the Stage 1 decision criteria were examined via simulation under binomial distributions with n=43 per treatment group (see Section 11.7).

Stage 2

The power to detect a duration response and the operating characteristics around estimating the minimum duration to achieve non-inferiority based on the upper bound of a 2-sided 95% CI for the difference (XBOS – 2HRZE/4HR) in unfavorable outcome rates being ≤12 percentage points was examined under various underlying true duration response profiles and sample size scenarios via clinical trial simulation.

See Section 11.7 for additional details regarding power and sample size calculations used to derive the sample sizes for the trial.

2. INTRODUCTION

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* (Mtb), which typically affects the lungs (pulmonary TB) but can affect other sites in the body as well (extrapulmonary TB). The unique waxy cell wall of Mtb, composed primarily of mycolic acids, allows the bacillus to lie dormant in some individuals for many years (ie, latent TB infection). While latent TB infection (LTBI) is not associated with symptoms and is not infectious, it confers a 5% to 15% lifetime risk of progression to active TB disease, sometimes occurring years or even decades after the initial infection (Gupta et al, 2020); individuals with LTBI who are co-infected with HIV are at greater risk of progressing to active TB (McShane et al, 2005; Zenner et al, 2017).

Nearly one-fourth of the world's population is estimated to have LTBI; among those infected, approximately 10 million people develop active TB each year and the disease disproportionately affects people in resource-limited settings, particularly those in Asia and Africa (WHO, 2021a). In 2019, at least 3 million of these individuals were undiagnosed or detected and not reported, and approximately 1.4 million died from TB placing it among the top three infectious diseases in terms of mortality (WHO, 2021a). With the global coronavirus disease-2019 (COVID-19) pandemic resulting in substantial disruptions to TB health services and the consequent increase in vulnerability to TB, TB incidence, and especially TB mortality, the WHO estimates that one-half million more people may have died from TB in 2020 alone due to the negative effects of the pandemic on global TB control, and TB incidence and mortality are projected to increase by around 5% to 15% through 2025, amounting to hundreds of thousands of additional TB deaths worldwide (McQuaid et al, 2021).

The current SOC for drug-sensitive (DS)-TB consists of an intensive phase of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by a continuation phase of 4 months of isoniazid and rifampicin (2HRZE/4HR; WHO, 2017a; Nahid et al, 2016). This combination was developed over a series of decades as new TB agents slowly came available and studies were performed to optimize their use (Fox et al, 1999). Each agent in the 4-drug combination serves an important purpose with rifampicin disrupting DNA transcription affecting both active and latent Mtb, pyrazinamide penetrating granuloma to block Mtb growth by disrupting the plasma membrane and energy metabolism, isoniazid disrupting mycolic acid synthesis, and ethambutol blocking cell wall synthesis and serving as a bacteriostatic agent to prevent emergence of resistant Mtb strains (NIH, 2021).

Though highly efficacious with relapse free cure rates of approximately 93% consistently achieved in clinical trials (Grace et al, 2019), treatment success achieved with 2HRZE/4HR by TB control and treatment programs globally overall ranges only 83% to 85% annually with considerably lower treatment success (71%) achieved in some higher burden countries such as South Africa and Brazil (WHO, 2021a). Several key issues are associated with administering this regimen effectively on a global scale. The duration and complexity may result in nonadherence, leading to suboptimal response (failure and relapse), ongoing transmission of infection in the community, and the emergence of resistance (WHO, 2021a). Further complicating treatment, rifampicin-based regimens are incompatible with some of the key anti-retroviral therapies (ART) used to treat HIV, a common co-infection in certain regions where TB is prevalent (WHO, 2021a). Additionally, the SOC is not without toxicity including hepatotoxicity and liver damage, gastrointestinal side-

effects, flu-like syndrome, renal dysfunction, nervous system side-effects, visual disturbances, myelosuppression, dermatologic side effects, and body fluid discoloration (Rifafour Product Label, 2018).

Resistance to rifampicin, as the most potent of the agents comprising 2HRZE/4HR, can reduce a patient's opportunity to achieve cure. TB resistant to at least rifampicin and isoniazid, known as multidrug resistant (MDR)-TB, has been particularly problematic for global TB control efforts. It requires treatment for a minimum of 6 months with the WHO-recommended BPaLM (bedaquiline, pretomanid, linezolid, moxifloxacin) or BPaL (bedaquiline, pretomanid, linezolid) regimens based on fluoroquinolone susceptibility, the all oral bedaquiline or linezolid based 9-month all oral regimen, or a longer 18-month individualized regimen based on a hierarchical grouping of second-line TB medicines, the drug-resistance profile and the patient's medical history; all treatment options require close medical monitoring. (WHO, 2022). Extensively drug resistant (XDR)-TB – with the recently updated definition of MDR-TB with added resistance to the fluoroquinolones and at least one additional Group A drug – further complicates treatment and disease control efforts (WHO, 2021b). Until the breakthrough and approval of the BPaL regimen, patients with XDR-TB (prior to 2021 defined as MDR-TB with added resistance to fluoroquinolones and an injectable anti-TB agent) had extremely limited options with treatment failure approaching 50% (Singh, 2019).

Approximately 410,000 MDR-TB cases (4% of global TB burden) occur annually with up to 10% of those occurring as XDR-TB (WHO, 2021a; WHO, 2023). The most recent global data on overall treatment outcomes among drug resistant patients – 57% achieved treatment success, 15% died, 16% were lost to follow up and 7% failed treatment (WHO, 2021a; WHO, 2023) – further highlight the urgent need for new regimens to transform treatment for all types of TB patients, enhance global TB control efforts, and accelerate on the path to TB elimination.

2.1. Trial Rationale

The goal for development of new TB treatment regimens is to identify combinations of agents (including new agents with novel mechanisms of action) that can substantially shorten treatment duration (≤3 months), have acceptable safety profiles limiting the need for close monitoring, are effective for both DS- and DR-TB ("pan-TB" regimen), and have low potential for drug-drug interaction with concomitant medications (eg, ART for HIV treatment).

The successful development of three new anti-TB drugs in recent years – bedaquiline (Sirturo® Product Label, 2023; Sirturo Summary of Product Characteristics (SmPC), 2021) by Janssen Pharmaceuticals, delamanid (Deltyba™ Summary of Product Characteristics [SmPC], 2023) by Otsuka Pharmaceutical Co, Ltd (Otsuka), and pretomanid (Pretomanid Product Label, 2022; Dovprela™ Summary of Product Characteristics [SmPC, 2023]) by the TB Alliance – all approved for use in adults with MDR-TB, raises the possibility of improved treatment regimens for TB, particularly if combined with new agents with novel mechanisms of action. Bedaquiline is from the novel diarylquinoline class that inhibits ATP generation in Mtb by interfering with the F-type adenosine triphosphate synthase activity. Delamanid and pretomanid are both from the nitroimidazole class of compounds which disrupt mycolic acid synthesis in Mtb crucial for cell wall integrity.

Combinations of bedaquiline plus pretomanid or delamanid, together with an oxazolidinone have the potential to form the backbone of a novel oral anti-TB drug regimen that may be able to substantially shorten the treatment for both DS- and DR-TB (a pan-TB regimen). The potential of this approach was recently demonstrated by the success of the BPaL single-arm Nix-TB trial in XDR-TB[1] and TI/NR-MDR-TB patients in South Africa in which bedaquiline and pretomanid were combined with the potent oxazolidinone, linezolid, to shorten the duration of therapy from more than two years down to 6 to 9 months with 90% of patients achieving cure (Conradie et al, 2020); these results supported approval of the BPaL-TB regimen for treatment of XDR-TB[1] patients and TI/NR MDR-TB patients (Pretomanid Product Label, 2022; Dovprela™ Summary of Product Characteristics, 2023) The success of this regimen built on very compelling results from a previous randomized controlled trial conducted in Korea, evaluating linezolid for XDR-TB patients with chronic disease refractory to multiple previous rounds of treatment; 79% of patients achieved sustained SCC by 4 months of treatment, and 71% achieved relapse free cure (as documented at one year after treatment completion) essentially from linezolid monotherapy (Lee et al, 2012; Lee et al, 2015). Additionally, acquired linezolid resistance was observed only in 11% of the 38 patients who received linezolid (Lee et al, 2015). This observed rate with monotherapy may be related to the infrequent emergence of resistance to this drug that has been observed in vitro (Hillemann et al, 2008). Although this represents a significant advance in the treatment of XDR-TB, BPaL's utility is limited by its safety profile (primarily due to the inclusion of the 1200 mg daily linezolid dose and the well-documented toxicities associated with use of linezolid for extended durations to achieve cure – including myelosuppression, peripheral neuropathy, etc.) (Lee et al, 2012; Conradie et al, 2020). The Nix-TB follow-on trial, ZeNix, evaluated 3 alternative linezolid dosing regimens of BPaL in a randomized, linezolid blinded trial, and demonstrated comparable efficacy but better safety and tolerability of shorter and/or lower doses of linezolid relative to the Nix-TB regimen (Conradie et al, 2022).

As recently demonstrated in the Tuberculosis Study Consortium (TBTC)/AIDS Clinical Study Group (ACTG) "Study 31" global treatment shortening trial conducted in DS-TB patients, the addition of a fourth agent (moxifloxacin) to the core 3-drug regimen of rifapentine, isoniazid, and pyrazinamide coupled with the optimization of dosing of rifapentine as a potent rifamycin was critical to achieving treatment shortening to 4-months relative to 6-months for 2HRZE/4HR as the SOC (Dorman et al, 2015; Dorman et al, 2020; Dorman et al, 2021; WHO, 2017a). This approach is further supported by compelling nonclinical and Phase 2b results indicating the potential for another 4-drug combination (bedaquiline, pretomanid, moxifloxacin, and pyrazinamide) to shorten treatment duration to 4-months or less in DS- and MDR-TB patients (Tweed et al, 2019). The

[1] The Nix-TB trial of the BPaL regimen was conducted before the revision of the definitions of XDR-TB and pre-XDR-TB in 2021 (WHO, 2021b). XDR-TB was previously defined as MDR-TB plus resistance to an anti-TB fluoroquinolone and an anti-TB injectable agent and pre-XDR-TB as MDR-TB plus resistance to either an anti-TB fluoroquinolone or an anti-TB injectable agent. Pretomanid was approved as part of the BPaL regimen for treatment of XDR-TB as defined pre-2021, which is now classified as pre-XDR-TB (MDR-TB plus resistance to an anti-TB fluoroquinolone).

TRUNCATE-TB trial which investigated four 2-month regimens that added or replaced 1-2 agents in HRZE (www.clinicaltrials.gov, NCT03474198) demonstrated that the bedaquiline–linezolid containing regimen was noninferior to HRZE with respect to clinical outcomes; the strategy was associated with a shorter total duration of treatment and with no evident safety concerns (Paton et al, 2023). An important limitation to the widespread use of these novel regimens is the presence of widespread resistance to one or more of their agents.

The proposed trial seeks to build on the successful development of BPaL in XDR-TB and MDR-TB patients with limited treatment options by using a backbone of bedaquiline and a nitroimidazole (pretomanid or delamanid) and replacing linezolid with the potentially safer and more efficacious investigational oxazolidinone, sutezolid. To maximize sterilizing potential and limit the emergence of resistance, the novel, potent inhibitor of the decaprenylphosphoryl β-D-ribose 2'-oxidase (DprE1) enzyme essential for Mtb cell wall biosynthesis, OPC-167832, from Otsuka will be added to the proposed 3-drug combinations to achieve the highest probability of successfully shortening treatment duration to ≤3 months.

2.1.1. Nonclinical Supportive Evidence

2.1.1.1.Relapsing Mouse Model

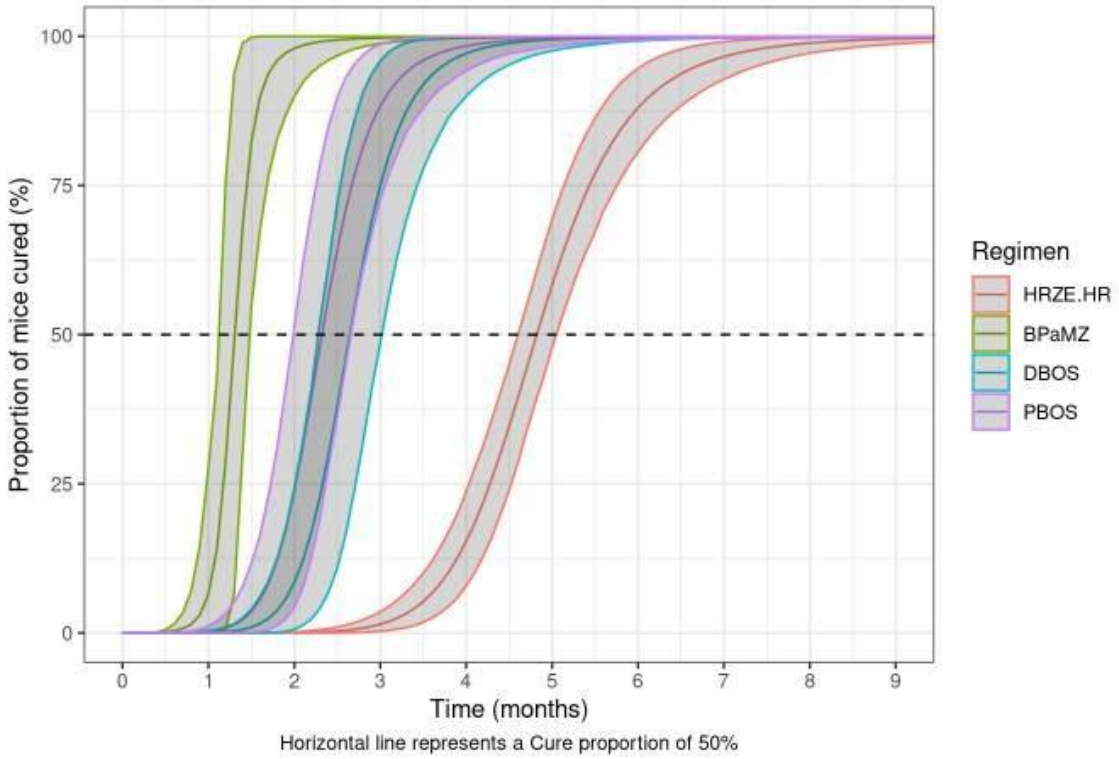
Recent data from an in vivo relapsing mouse model (RMM) study evaluating the DBOS and PBOS regimens support the rationale for TB regimen construction in this trial of adding a fourth anti-TB agent to the proven TB treatment benefit from a backbone regimen of a diarylquinoline, a nitroimidazole, and an oxazolidinone agent. In this study, BALB/c mice were infected with a high-dose aerosol of Mtb Erdman and treated after 11 days with DBOS, PBOS, or one of 2 control regimens: HRZE or the best performing TB regimen to date in RMM studies, BPaMZ (bedaquiline, pretomanid, moxifloxacin, and pyrazinamide). Bactericidal activity was assessed following 2, 4, 6, 8 and 10 weeks of treatment. Relapse prevention was measured using groups of companion mice sacrificed 3 months after cessation of drug therapy. This study incorporated the "Erasmus-Cognigen" design which includes more frequent sampling of smaller numbers of mice and regression analysis and modelling of the resultant data to better calculate true relapse probability and time profiles. From this model, regimens are considered effective when treatment duration is shortened by at least 1-2 months relative to the 6-month HRZE regimen.

The results from the study demonstrated that the DBOS, PBOS, and BPaMZ regimens were all more bactericidal than HRZE and no statistically significant differences in performance between DBOS or PBOS were detected at any of the timepoints assessed based on bactericidal response.

In the study, all regimens showed significant improvement in treatment shortening compared to HRZE which routinely achieves durable cure with no relapse after 5-6 months of therapy in the BALB/c RMM; BPaMZ shortened the time to durable cure by at least 3.5 months, which is consistent with previous RMM studies including that regimen (Xu et al, 2019), and the DBOS and PBOS regimens shortened the time to cure by at least 2.5 months. Of note, the BPaMZ regimen is being evaluated in the Phase 2c SimpliciTB trial administered for 4 months in DS-TB patients and 6 months in DR-TB patients with published results expected in 2024 (www.clinicaltrials.gov, NCT03338621).

Figure 2 shows the results from the mathematical modelling and regression analysis of the study data, which clearly demonstrates the superiority of DBOS and PBOS compared with HRZE. A model-based meta-analysis approach provided the framework to compare the efficacy of the DBOS, PBOS, BPaMZ, and HRZE treatment regimens (Berg et al, 2022).

Figure 2 Relapse Probability Versus Treatment Duration for DBOS, PBOS, BPaMZ, and HRZE Regimens in BALB/c Relapsing Mouse Model



Smooth lines and shaded areas represent the median and 95% confidence intervals.

2.1.1.2.Hollow Fiber System

The Hollow Fiber System Model of Tuberculosis (HFS-TB) – which builds on the principles of Hollow Fiber Bioreactor System technology used to assess activity of anti-bacterial agents (De Napolia, 2014) – serves as a useful in vitro preclinical tool for optimization of dose selection and drug regimens in anti-TB drug development (EMA, 2015). The potential efficacy of the regimens to be evaluated in this trial is supported by HFS-TB data from a study conducted by Praedicare Laboratories (www.praedicarelabs.com), Dallas, TX, which demonstrated that the combination of 4 drugs in a regimen can potentiate treatment duration shortening (Table 5). Based on the results of this 28-day study, DBOS, DBO, and BPMZ have the shortest time-to-achieve extinction (TTE), and both demonstrate a significant improvement over standard therapy (2HRZE/4HR; historical data) and HRZ (In-study control) as shown in the table below (Magombedze et al, 2018).

In Table 6, simulation results are featured from a separate data modeling analysis, generated by the 28-day Praedicare study. This analysis was conducted to calculate TTE for the regimens under different mixture distributions of log-phase and semi-dormant bacteria prior to treatment

initiation; results in the Praedicare study featured in Table 5 were generated with the pre-treatment bacterial population set at 77% log-phase and 23% semi-dormant. Two key assumptions differing from the Praedicare study were used to support the simulations in this analysis – the first is that a transition rate from fast growing to semi-dormant bacteria occurs in the bacterial mixture over time with treatment (De Groote et al, 2011; Gumbo et al, 2015; Kramnik et al, 2016; Chen et al, 2017; Doan et al, 2018) and the second is that no treatment effect occurs on growth suppression; treatment effect in this analysis is primarily on bacterial killing. This model provides a fit-for-purpose approach to representing the drug/regimen effect on bacteria, including both bacteriostatic and bactericidal behaviors and adds to the robustness of results from the original Praedicare study. Based on the simulations with proportion of pre-treatment bacterial population in log-phase varied from 10% to 90% for the 28-day study, DBOS and BPMZ have the shortest TTE, and both demonstrate a significant improvement over the HRZ in-study control regimen. Additionally, the added value of the four agents combined to form DBOS are further demonstrated with TTE decreasing for the 4-drug DBOS combination as compared to the 3-drug combinations of DBO and DOS.

Table 5 Time-To-Extinction (Days) Based on Combined Bactericidal and Sterilizing Effect of Combination Regimens Generated in Hollow Fiber System Model of Tuberculosis

Parameter	Standard[I] (HRZ)	HRZE[‡]	BPaMZ	PaMZ	BPaZ	DBOS	DOS	DBO	DO	BO
TTE-HFS	25.3 (19.4-43.7)	23.1 (1.1)	15.0 (14.4-20.4)	19.2 (16.5-24.4)	28.2 (24.2-45.2)	15.2 (15.2-18.8)	19.8 (16.4-25.6)	15.0 (14.9-20)	15.6 (15.1-22.9)	20.4 (16.9-27)

[I]In study standard; [‡]Historical data
Source: Magombedze et al, 2018

Table 6 Time to Extinction (Days) Based on a Mixture Model of Bactericidal and Sterilizing Distributions and Respective Regimen Kill Rates

Regimen	Mean TTE 10% Log-phase	Mean TTE 50% Log-phase	Mean TTE 70% Log-phase	Mean TTE 90% Log-phase
BPaZ	27.98	27.41	26.95	26.84
PaMZ	15.05	15.96	16.25	16.62
BPaMZ	13.38	15.03	15.42	15.83
HRZ	28.07	27.36	26.75	26.42
BO	15.22	16.21	16.52	16.89
DBO	20.55	20.18	19.88	19.81
DO	27.38	26.68	26.08	25.76
DOS	15.75	16.51	16.78	17.12
DBOS	15.53	15.49	15.45	15.56

The proposed regimens to be evaluated in the trial - DBOS (delamanid + bedaquiline + OPC-167832 + sutezolid) and PBOS (pretomanid + bedaquiline + OPC-167832 + sutezolid) have not previously been evaluated in clinical development, but as outlined in Section 3, their evaluation as potential treatment shortening regimens is supported by the totality of available clinical and nonclinical data from the individual agents comprising the regimens and from assessment of them

in various combinations. As they have not been evaluated clinically, careful safety monitoring will be performed.

3. KNOWN AND POTENTIAL BENEFIT/RISKS

3.1. Marketed Products

3.1.1. Bedaquiline

3.1.1.1. MDR-TB

3.1.1.1.1. Bedaquiline Efficacy

Bedaquiline was first approved in 2012 by the FDA as part of combination treatment for adults with pulmonary MDR-TB. Beyond adults, it is now also approved by the FDA and the EMA for adolescents and children (≥5 years and ≥15 kg). In the pivotal trial for initial registration, bedaquiline administered in combination with a suitable background treatment regimen for MDR-TB reduced the median time to SCC, as compared with the group receiving placebo in combination with the background regimen, from 125 days to 83 days (hazard ratio in the bedaquiline group, 2.44; 95% confidence interval, 1.57 to 3.80; P<0.001 by Cox regression analysis) and increased the rate of SCC at 24 weeks (79% vs. 58%, P=0.008) and at 120 weeks (62% vs. 44%, P=0.04). Cure rates at 120 weeks were 58% in the bedaquiline group and 32% in the placebo group (P=0.003) (Diacon et al, 2014).

An individual patient data meta-analysis of 12,030 patients from 25 countries in 50 studies entering treatment for MDR-TB during the 2000's and early 2010's showed treatment with bedaquiline was positively associated with treatment success compared with failure or relapse (adjusted risk difference 0.10, 95% confidence interval, 0.05 to 0.14), along with several other drugs (linezolid, levofloxacin, carbapenems, and moxifloxacin). In addition, a significant association was identified between reduced mortality and the use of bedaquiline (adjusted risk difference -0.14, 95% confidence interval, -0.19 to -0.10) (Schnippel et al, 2018; Collaborative Group for the Meta-Analysis of Individual Patient Data in MDRTB, 2018; Mbuagbaw et al, 2019).

3.1.1.1.2. Bedaquiline Safety

In terms of safety, in the pivotal trial supporting bedaquiline's registration, the overall incidence of AEs was similar in the investigational and control groups. However, 9 deaths occurred in the bedaquiline group and 2 in the placebo group, with no causal pattern evident. One death in the investigational arm occurred during the 24 weeks of administration of bedaquiline and the remainder occurred in the follow up period (Diacon et al, 2014). The most common adverse reactions, reported in >10% of patients in controlled trials, were nausea, arthralgia, headache, hemoptysis, and chest pain. More broadly, bedaquiline prolongs the QT interval of cardiac conduction and has been associated with hepatic toxicity, including elevations in alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), alkaline phosphatase, and bilirubin. Patients on bedaquiline require monitoring of their QTc interval and hepatic function and should have electrolytes tested at the start of treatment and in the event of an increase in the QTc interval (Sirturo® Product Label, 2023).

An evaluation of data from an active drug safety monitoring (aDSM) system of the New Drug Introduction and Protection Program (NDIP) established in China according to WHO recommendations for pharmacovigilance for introducing new drugs and regimens for drug resistant TB provides important insight into the use of bedaquiline in the context of a large national

treatment program. From this evaluation, data on the frequency and severity of AEs of bedaquiline-containing regimens are available to address safety concerns raised in the pivotal trial supporting initial registration of bedaquiline (Gao et al, 2021). In this evaluation, AEs were prospectively collected with demographic, bacteriological, radiological and clinical data from 54 sites throughout China at patient enrollment and during treatment between February 2018 and December 2019. The analysis included 1162 patients who had received bedaquiline-containing anti-TB treatment and included those who had either completed treatment or were still on treatment as of 31 December 2019. The median duration of bedaquiline treatment was 167.0 (interquartile range [IQR]: 75–169) days. Eight-six (7.4%) patients received 36-week prolonged treatment with bedaquiline. Overall, 1563 AEs were reported, of which 66.9% were classified as minor (Grade 1-2) and 33.1% as serious (Grade 3–5). The incidences of AEs and serious AEs were 47.1% and 7.8%, respectively. The most frequently reported AEs were QT prolongation (24.7%) and hepatotoxicity (16.4%). There were 14 (1.2%) AEs leading to death. Among patients with available QT interval corrected by Fridericia's formula (QTcF) data, 3.1% (32/1044) experienced a post-baseline QTcF ≥500 ms, and 15.7% (132/839) had at least one change of QTcF ≥60 ms from baseline. Fifty-nine (4.2%) patients had an AE of QT prolongation reported leading to bedaquiline withdrawal. With respect to hepatotoxicity, 190 patients reported 361 AEs; 34 patients reported 43 AEs of hepatic injury attributed to bedaquiline, much lower than that attributed to the other anti-TB agents used in treatment regimens (prothionamide, pyrazinamide and para-aminosalicylic acid).

Overall, real-world safety data using bedaquiline in diverse populations that frequently have significant co-morbidities and complicated concomitant medications (eg, clofazimine, moxifloxacin) (Brust et al, 2021) has not identified any new safety signals in addition to QT prolongation and hepatotoxicity and, in fact, has demonstrated a mortality benefit from the use of bedaquiline (Olayanju et al, 2018; Ndjeka et al, 2018). Additional cohorts and case reports suggest that concomitant medications are most often the primary drivers of QT prolongation and hepatotoxicity, and bedaquiline has been able to be continued in nearly all patients (Olayanju et al, 2018; Brust et al, 2021). These data supported WHO's recent recommendations to expand the use of bedaquiline for treatment of drug resistant TB. Combining bedaquiline with TB agents that have less pronounced overlapping toxicities, such as those proposed in this trial, could yield significant reductions in the frequency of these adverse events.

See Section 3.2.3 for discussion of potential for drug-drug interactions with bedaquiline.

3.1.1.1.3. DS-TB

With respect to DS-TB, in the randomized 14-day early bactericidal activity (EBA) trial of bedaquiline administered as monotherapy to four groups of patients in doses of 100, 200, 300, and 400 mg on treatment Days 3 to 14, preceded by single daily loading doses of 200, 400, 500, and 700 mg, respectively, on treatment Day 1 and 100, 300, 400, and 500 mg, respectively, on treatment Day 2, all groups showed activity with a mean (standard deviation) daily fall in $\log_{10}$ CFU over 14 days of 0.040 (0.068), 0.056 (0.051), 0.077 (0.064), and 0.104 (0.077) in the 100, 200, 300, and 400-mg groups, respectively (Diacon et al, 2013).

Available data on the efficacy and safety from the longer-term use of bedaquiline in treatment of DS-TB have been generated almost entirely in combination studies with pretomanid, including a controlled trial assessing the impact of treatment with two different dosing regimens of bedaquiline, in combination with pretomanid, and pyrazinamide on SCC after 8 weeks of treatment (Tweed et al, 2019); results from this assessment are featured in Section 3.3.2.1 and provide additional supportive evidence for use of bedaquiline in treatment of DS-TB. Additionally, an open-label, partially randomized trial to evaluate the efficacy and safety of treatment with bedaquiline in combination with pretomanid, moxifloxacin and pyrazinamide (BPaMZ) administered for 4 months in DS-TB(www.clinicaltrials.gov; NCT03338621) completed in 2022 validated observations from pre-clinical relapsing mouse model experiments which identified BPaMZ as a regimen with high efficacy and treatment shortening potential, but hepatic toxicity precluded treatment completion in approximately 6-7% of patients (Eristavi et al, 2023). A complementary multi-study analysis showed that Pa-Z-containing regimens were associated with a hepatic safety profile distinct from BPaL, with a higher incidence and degree of grade 4 alanine transaminase elevations. A separate open-label, randomized trial to evaluate the 14-day efficacy and safety of bedaquiline combined with OPC-167832 as well as bedaquiline combined with OPC-167832 and delamanid in DS-TB demonstrated that the combinations were well tolerated and the three-drug combination exhibited similar early bactericidal activity to HRZE supporting further evaluation for longer term treatment (www.clinicaltrials.gov; NCT03678688; Dawson et al, 2023b).

3.1.2. Delamanid

3.1.2.1. MDR-TB

3.1.2.1.1. Delamanid Efficacy

Delamanid was first approved in Europe (by the EMA) in 2014 as part of combination treatment for adults with pulmonary MDR-TB. It is now also approved for adolescents, children, and infants (≥10 kg). In the pivotal trial for initial registration, delamanid administered as 100 mg twice daily in combination with an optimized background drug regimen (OBR) in participants with MDR-TB achieved 45.4% sputum culture conversion at 2 months, as compared with 29.6% of patients who received the background drug regimen plus placebo (P=0.008) (Gler et al, 2012).

In the observational cohort study conducted to capture final treatment outcomes at 24 months post-randomization for patients who participated in the pivotal trial assessing the impact of delamanid on SCC during treatment, efficacy results were compelling (Skripconoka et al, 2013). In total, 421/481 (87.5%) patients who were randomized in the original pivotal trial granted consent for follow-up assessments. Among these, favorable outcomes were observed in 143/192 (74.5%) patients who received delamanid for 6 months, compared to 126/229 (55%) patients who received delamanid for 2 months or less. Mortality was reduced to 1.0% among those receiving long-term delamanid versus short-term/no delamanid (8.3%; p, 0.001). Treatment benefit was also seen among the subset of XDR-TB patients enrolled in the study (Gupta et al, 2015).

In a subsequent large global trial also in MDR-TB, median time to SCC was 51 days (IQR 29-98) among participants receiving delamanid (100 mg BID for 2 months followed by 200 mg QD for 4 months) plus OBR versus 57 days (IQR 43–85) among participants receiving placebo plus OBR (P=0.0562; modified Peto-Peto) (Von Groote-Bidlingmaier et al, 2019).

In a post-hoc analysis of data from this trial, development of resistance to OBR medications was less frequent in the delamanid plus OBR group than the placebo plus OBR group, including first-line SOC medications including pyrazinamide - 1.2% versus 5.1% and ethambutol - 3.7% versus 9.4%, injectable agents including streptomycin - 0% versus 1% and other injectable agents - 5.2% versus 6%, and fluoroquinolones including ofloxacin - 3% versus 3.7% and moxifloxacin or levofloxacin - 1.1% versus 3.5%.

3.1.2.1.2. Delamanid Safety

In terms of safety, in the pivotal trial supporting delamanid's registration as a treatment agent for MDR-TB, most AEs were mild to moderate in severity and were evenly distributed across groups. Although no clinical events due to QTcF prolongation on electrocardiography were observed, QTcF prolongation was reported significantly more frequently in the group that received delamanid 100 mg twice daily (9.9%) compared to the placebo group (3.8%) (Gler et al, 2012). The greatest mean placebo-corrected QTcF increase from baseline was 12.1 milliseconds. The most common (≥10%) AEs in patients treated with delamanid plus OBR were nausea (32.9%), vomiting (29.9%), insomnia (27.3%), dizziness (22.4%), tinnitus (16.5%), hypokalemia (16.2%), gastritis (15.0%), decreased appetite (13.1%), and asthenia (11.3%).

With respect to safety results from the subsequent global study that followed the pivotal trial, 501 (98.0%) of 511 patients had at least 1 treatment-emergent AE (TEAE) and 136 (26.6%) of 511 patients had at least 1 serious TEAE; the incidence was similar between treatment groups (89 [26.1%] of 341 patients for delamanid plus OBR and 47 [27.6%] of 170 for placebo plus OBR). Deaths related to TEAEs were similar between groups (15 [4.4%] of 341 for delamanid and 6 [3.5%] of 170 for placebo); no deaths were considered related to delamanid. The greatest mean placebo-corrected QTcF increase from baseline was 5.9 milliseconds at 5 weeks of delamanid plus OBR treatment (Von Groote-Bidlingmaier et al, 2019).

Across 4 completed studies of participants with MDR-TB treated with delamanid, the only TEAE that led to the discontinuation of trial drug in more than 1 participant in the DLM plus OBR group was prolonged ECG QT interval (7 participants in the DLM plus OBR group and 2 participants in the placebo plus OBR group). The serious TEAEs that occurred in at least 1% of participants in the DLM plus OBR group and at a higher incidence than in the placebo plus OBR group were prolonged ECG QT interval (3.4% DLM + OBR, 1.2% placebo + OBR), TB (2.1% DLM + OBR, 0.9% placebo plus OBR), and hypokalemia (1.6% DLM + OBR, 0.9% placebo plus OBR).

Additionally, several psychiatric adverse drug reactions have been described for delamanid, including psychotic disorder, anxiety, depression, and hallucinations. Cases of hallucination have predominantly been reported in the pediatric population in post-marketing surveillance though were observed in 5.4% of children in delamanid clinical trials and 1% of adults (Deltyba™ SmPC, 2023).

See Section 3.2.3 for discussion of potential for drug-drug interactions with delamanid.

3.1.2.2. DS-TB

With respect to DS-TB, in the 14-day early bactericidal trial of delamanid that evaluated 100, 200, 300, and 400 mg daily administered as monotherapy, 70% of participants receiving 200 mg and

80% of those receiving 300 mg achieved ≥0.9 $\log_{10}$ CFU/mL sputum decline compared to 45% and 27% of those receiving 100 and 400 mg, respectively (Diacon et al, 2014). Delamanid exposure was less than dosage-proportional, reaching a plateau at 300 mg, likely due to dose-limited absorption. A moderate but significant correlation was found between C_{max} and EBA, indicating exposure dependence. Delamanid was well-tolerated in this patient population without significant toxicity. There were 5 serious TEAEs (3 events of prolonged ECG QT interval and 2 events of increased transaminases); however, no deaths occurred, and no participants discontinued trial drug due to TEAEs (Deltyba™ SmPC, 2023).

An open-label, randomized trial to evaluate the 14-day efficacy and safety of delamanid combined with OPC-167832 as well as delamanid combined with OPC-167832 and bedaquiline in DS-TB was completed and the combination exhibited similar early bactericidal activity to HRZE supporting further evaluation for longer term treatment (Dawson et al, 2023b; www.clinicaltrials.gov, NCT05221502).

3.1.3. Pretomanid

3.1.3.1. MDR-TB

Pretomanid was first approved by the FDA as part of a combination regimen with bedaquiline and linezolid in 2019 for adults with TI/NR MDR-TB and XDR-TB (Pretomanid Product Label, 2022). In the pivotal trial used for initial registration, 109 participants with XDR-TB and TI/NR MDR-TB were enrolled in an open-label single cohort trial to evaluate the efficacy and safety of this 3-drug regimen administered for 6 months compared to historical controls. In the intent-to-treat analysis, at 6 months after the end of treatment 98 patients (90%; 95% confidence interval, 83% to 95%) had a favorable outcome treatment and 11 patients (10%) had an unfavorable outcome (Conradie et al, 2020); substantially lower treatment success for XDR-TB patients in South Africa was reported prior to the conduct of the trial (Olayanju et al, 2018). Results from the follow-on ZeNix trial that investigated 4 different linezolid dosing strategies (1200 mg daily for 6 months, 1200 mg daily for 2 months, 600 mg daily for 6 months, and 600 mg daily for 2 months) within the BPaL regimen demonstrated similar overall efficacy results with 89% of participants (range among treatment arms of 84% to 93%) having a favorable outcome at 6 months after 6 months of BPaL treatment (Conradie et al, 2022).

In terms of safety among MDR-TB and XDR-TB patients, from the pivotal trial supporting pretomanid's registration, the expected linezolid toxic effects of peripheral neuropathy (occurring in 81% of patients) and myelosuppression (48%), were common and often led to dose reductions or interruptions in treatment with linezolid (Conradie et al, 2020).

Additionally, of the 109 participants in the pivotal trial, 12 (11%) developed ALT levels above 3 times the upper limit of normal (ULN) of whom two also developed mild jaundice (bilirubin above twice but less than 3 times ULN) arising during month two of therapy. Both patients had mild nausea accompanying the liver test abnormalities, and the abnormalities resolved in both with temporary interruption in treatment, followed by re-initiation using lower dose linezolid without change in the pretomanid or bedaquiline dose. Most AEs were attributed to linezolid (Conradie et al, 2020).

See Section 3.2.3 for discussion of potential for drug-drug interactions with pretomanid.

3.1.3.2. DS-TB

3.1.3.2.1. Pretomanid Efficacy

Six completed trials have evaluated treatment of DS-TB with pretomanid: two EBA trials where pretomanid was given as monotherapy for 14 days and four trials where pretomanid was administered in combination with 1 to 2 other anti-TB drugs. The initial EBA monotherapy trial evaluated pretomanid doses of 200, 600, 1000, and 1200 mg and demonstrated clear bactericidal activity over 14 days at all doses (mean daily $\log_{10}$ CFU/mL decline of 0.098 [standard deviation [SD] ±0.072]) with no clear delineation between doses (Diacon et al, 2010). A subsequent EBA trial evaluated lower doses of pretomanid (50, 100, 150, and 200 mg) and again demonstrated bactericidal activity at all doses: mean daily $\log_{10}$ CFU/mL decline of 0.063 (SD 0.058) in 50 mg arm, 0.091 (0.073) in 100 mg arm, 0.078 (0.074) in 150 mg arm, and 0.112 (0.070) in 200 mg arm (Diacon et al, 2012a). A non-significant (P=0.0605) trend of greater activity achieved with higher pretomanid doses was observed. An additional 14-day EBA trial evaluated 200 mg of pretomanid given in combination with 1 to 2 other anti-TB agents (with bedaquiline [BPa], with pyrazinamide [PaZ], or with moxifloxacin and pyrazinamide [PaMZ]) as well as two other combinations (bedaquiline and pyrazinamide [BZ] and HRZE) and bedaquiline monotherapy. Bactericidal activity as measured by mean daily $\log_{10}$ CFU/mL decline was greatest in the PaMZ arm (0.233 [SD 0.128]) followed by PaZ (0.154 [0.040]), HRZE (0.140 [0.094]), BZ (0.131 [0.102]), BPa (0.114 [0.050]), and then bedaquiline (0.061 [0.068]) (Diacon et al, 2012b).

A Phase 2b trial of bactericidal activity (BA) over 8 weeks - defined as the average decrease in CFUs of Mtb in sputum - conducted in South Africa and Tanzania with results reported in 2015 showed encouraging results building upon the previous EBA trial results (Dawson et al, 2015); pretomanid administered as 200 mg daily in combination with moxifloxacin and pyrazinamide (PaMZ) for 8 weeks was safe, well-tolerated and showed superior BA compared to HRZE (0.155 $\log_{10}$CFU decline/day [95% Bayesian credibility interval 0.133-0.178] vs. 0.122 $\log_{10}$CFU decline/day [0.093-0.131]).

A second Phase 2b trial assessed 8 weeks of 200 mg daily of pretomanid with pyrazinamide 1500 mg daily and bedaquiline (BPaZ) in DS-TB patients (Tweed CD). Of note, bedaquiline was administered in two different dosing strategies: the product label dosing regimen of 400 mg daily for 2 weeks then 200 mg thrice weekly (B_{load}PaZ) or 200 mg daily without a loading dose (B_{200}PaZ). Eight weeks of HRZE was the active DS-TB control arm. An observational arm of RR-TB patients enrolled in the same trial received BPaMZ. The primary outcome was daily percentage change in time to positivity (TTP) in liquid sputum culture over the 8 weeks of trial treatment. B_{200}PaZ demonstrated the highest daily change in percentage TTP (5.17%, 95% Bayesian credibility interval 4.61-5.77) followed by B_{load}PaZ (4.87%, 4.31-5.47) then HRZE (4.04%, 3.67-4.42); the changes in TTP in both BPaZ arms were significantly higher than HRZE.

In the Shortening Treatment by Advancing Novel Drugs (STAND) trial conducted in DS-TB which followed up on the results of the Phase 2b BA trial, multiple doses and durations of treatment of pretomanid administered in combination with moxifloxacin and pyrazinamide (PaMZ) were evaluated in comparison to 2HRZE/4HR (Tweed et al, 2021). Two doses of pretomanid were

assessed for 4 months (100 mg [4Pa$_{100}$MZ] and 200 mg daily [4Pa$_{200}$MZ]) and pretomanid 200 mg daily was also assessed for 6 months (6Pa$_{200}$MZ). Pyrazinamide was administered throughout the treatment course for all three experimental pretomanid-containing arms but only for the first 2 months of treatment in 2HRZE/4HR as per treatment guidelines. The primary composite endpoint was unfavorable outcome at 12 months post randomization. Favorable treatment outcomes occurred among 66.7% (38/57) of 4Pa$_{100}$MZ participants, 75.4% (46/61) of 4Pa$_{200}$MZ participants, and 76.8% (43/56) of 6Pa$_{200}$MZ participants in comparison with 86.7% (52/60) of 2HRZE/4HR participants (Tweed et al, 2021).

The open-label, partially randomized trial to evaluate the efficacy and safety of treatment with pretomanid (200 mg) in combination with bedaquiline, moxifloxacin and pyrazinamide (BPaMZ) administered for 4 months in DS-TB validated observations from pre-clinical relapsing mouse model experiments identifying BPaMZ as a regimen with high efficacy and treatment shortening potential, but hepatic toxicity precluded treatment completion in approximately 6-7% of patients; a complementary multi-study analysis showed that Pa-Z-containing regimens were associated with a hepatic safety profile distinct from BPaL, with a higher incidence and degree of grade 4 ALT elevations.(www.clinicaltrials.gov, NCT03338621; Eristavi et al, 2023).

3.1.3.2.2. Pretomanid Safety

In the safety analysis from the STAND trial, higher proportions of TEAE and serious AEs were observed in the experimental arms (PaMZ) than in the standard TB regimen among DS-TB participants that were most commonly hepatic in nature. Overall, 11% of DS-TB participants receiving experimental regimens demonstrated a peak ALT ≥5 x ULN versus 6% of participants allocated to the standard TB regimen. Importantly, 11% of participants in PaMZ arms had to stop treatment early due to a TEAE compared to 6% in the standard treatment arm, and 3 deaths among participants receiving PaMZ regimens were attributed to hepatotoxicity deemed possibly related to PaMZ. Table 7 provides a summary of mortality rates, SAEs, treatment discontinuations and liver-related AEs from the trial results.

Table 7 Mortality, Serious Adverse Events, and Hepatic Toxicity From the Shortening Treatment by Advancing Novel Drugs (STAND) Trial[†]

	Pretomanid (100) (+ Moxifloxacin + Pyrazinamide) 4 Months	Pretomanid (200) (+ Moxifloxacin + Pyrazinamide) 4 Months	Pretomanid (200) (+ Moxifloxacin + Pyrazinamide) 6 Months	2HRZE/4HR
All-cause mortality	4/65 (6.2%)	3/71 (4.2%)	3/67 (4.5%)	2/68 (2.9%)
≥1 SAE	3 (4.6%)	8 (11.3%)	8 (11.9%)	3 (4.4%)
Early treatment discontinuation due to TEAE	6 (9.2%)	6 (8.5%)	11 (16.4%)	4 (5.9%)
≥1 liver-related SAE	1 (1.5%)	4 (5.6%)	4 (6%)	0 (0%)
≥1 liver-related TEAE	19 (29.2%)	17 (23.9%)	24 (35.8%)	21 (30.9%)
ALT increased	13 (20%)	11 (15.5%)	18 (26.9%)	11 (16.2%)
AST increased	15 (23.1%)	11 (15.5%)	18 (26.9%)	17 (25%)
Peak ALT >5x ULN	4 (6.2%)	9 (12.6%)	10 (14.9%)	4 (5.9%)
Peak ALT >10x ULN	4 (6.2%)	5 (7%)	5 (7.5%)	2 (2.9%)

[†]Source: adapted from Tweed et al, 2021

A full review of the safety data relating to the trial, and the earlier Phase 2 trial, was undertaken and included external specialists in hepatotoxicity and the Data Safety Monitoring Committee (DSMC) commissioned to safeguard participants for the trial. No conclusive evidence was found supporting an unduly increased risk for severe drug-induced liver injury (DILI) in the experimental arms. Delayed recognition of DILI and subsequent withdrawal of possible offending drugs were identified as contributing factors in the deaths. The DSMC subsequently recommended resuming enrollment in the trial with additional safety monitoring in place; however, the Sponsor decided instead to pursue a Phase 3 clinical trial of a combination of bedaquiline with the $Pa_{200}MZ$ regimen that had demonstrated very promising bactericidal activity (Tweed et al, 2021).

A pooled safety analysis of all trials evaluating pretomanid combination therapy in DS-TB patients showed the most frequent (>10%) TEAEs occurring in 534 participants receiving a pretomanid-containing regimen were hyperuricemia (28%), arthralgia (21%), elevated ALT/AST (18%), and nausea (12%). Hyperuricemia (25%), arthralgias (14%), and ALT/AST elevations (13%) were also common in the 229 participants that received HRZE in these trials. Hyperuricemia and arthralgias are well-described adverse effects of pyrazinamide, which was co-administered in most of these DS-TB patients receiving pretomanid combination therapy. The most frequently occurring (>2% of participants) severe (Grade 3) or life-threatening (Grade 4) TEAEs in participants receiving pretomanid combination therapy were hyperuricemia (8%), elevated ALT (8%), elevated AST (8%), and elevated GGT (4%). There were no deaths among DS-TB patients receiving pretomanid combination therapy attributed to hepatotoxicity beyond the 3 deaths reported in the STAND trial (U.S. Food and Drug Administration, 2022a).

3.1.3.2.2.1. Risk of Testicular Toxicity

Pretomanid causes testicular toxicity in mice and rats characterized by degeneration/atrophy. Serum levels of male reproductive hormones are altered in association with this injury. Assessment of effects on rat fertility showed no effect on male or female libido but there was impaired fertility ascribed to male mediated effects.

There were no histopathological effects on male or female reproductive organs in monkeys attributed to pretomanid in two 3-month and one 9-month toxicity studies. No pretomanid-related alterations in male reproductive hormones were observed. Decreased sperm motility, total sperm count, and increased abnormal sperm ratio were observed in monkeys in the highest dosing groups (150 and 300 mg/kg/day) in a 3-month GLP study but not in the lowest dosing group (50 mg/kg/day). In the absence of histopathological changes in the testes or epididymides, these semen changes were attributed as secondary to general adverse effects from the higher doses, and the majority of the changes were reversible.

The effect of pretomanid on sex hormones in male participants (follicle-stimulating hormone, luteinizing hormone, inhibin B, and testosterone) was evaluated in 4 pretomanid-containing clinical trials, including one of 26 weeks duration. Overall, these hormone assessments demonstrated an improvement in the underlying hypogonadism, as reflected by increases in testosterone and inhibin B levels, in all treatment arms, consistent with improvements in the underlying disease state. In addition, no adverse events associated with fertility disorders among male participants were identified across 19 studies in the pretomanid clinical development program (Pretomanid Investigator's Brochure, 2023).

A retrospective survey of male participants that had received pretomanid in 4 studies or HRZE in 2 studies was conducted to evaluate the number of partner births that had occurred while the male participant had received pretomanid or HRZE or afterwards. The adjusted rate ratio of incidences of fathering at least 1 child after the start of study treatment was 0.98 (95% CI 0.47, 2.03, p=0.957) suggesting pretomanid does not have an effect on fertility compared with HRZE (Pretomanid Investigator's Brochure, 2023).

A 6-month study focused on addressing the reproductive safety of pretomanid in adult male DR-TB patients receiving the BPaMZ regimen has completed enrollment with results on the primary endpoint of change in sperm count from baseline to week 26 included in the current Investigator's Brochure. The mean total sperm count and sperm concentration increased from baseline throughout treatment to week 26 with no change in semen volume. These results suggest treatment with a pretomanid-containing regimen for up to 6 months does not adversely affect human spermatogenesis. Full trial results are expected in 2024 (Pretomanid Investigator's Brochure, 2023; www.clinicaltrials.gov; NCT04179500).

The potential risk for testicular toxicity will be highlighted during the informed consent process for males being screened for participation in this clinical trial.

3.2. Investigational Products

3.2.1. OPC-167832

OPC-167832 is a novel 3,4-dihydrocarbostyril derivative discovered by Otsuka through their anti-TB agent screening program and is currently in Phase 2 development. It has a novel mechanism of action as an inhibitor of decaprenylphosphoryl β-D-ribose 2'-oxidase (DprE1), an essential enzyme for Mtb cell wall biosynthesis, confirmed through whole-genome and targeted sequencing of Mtb isolates resistant to OPC-167832.

3.2.1.1. Nonclinical

The MIC of OPC-167832 for Mtb on clinical DS-, MDR-, and XDR-TB strains ranges from 0.00024 to 0.002 μg/mL. The frequency of spontaneous resistance of OPC-167832 was 2.60×10^{-9} to 1.52×10^{-7} for MTB H37Rv at 16 × MIC (Hariguchi et al, 2020). In vitro and in vivo studies have shown that OPC-167832 has potent bactericidal activity against both growing and intracellular bacilli (Hariguchi et al, 2020).

In a mouse model of chronic TB, OPC-167832 showed potent bactericidal activities starting at a dose of 0.625 mg/kg of body weight. It exhibited significant combination effects in 2-drug combinations with delamanid, bedaquiline, or levofloxacin. Additionally, 3- or 4-drug regimens comprised of delamanid and OPC-167832 as the core along with bedaquiline, moxifloxacin, or linezolid showed efficacy in reducing the bacterial burden and preventing relapse superior to that of the SOC regimen (HRZE). No antagonistic activity has been shown with OPC-167832 and delamanid or bedaquiline (Hariguchi et al, 2020). The No-Observed-Adverse-Effect Levels (NOAELs) for OPC-167832 in chronic studies were observed at exposures that were significantly above the highest human exposures in Phase 1 studies. Risk for additive or synergistic toxicities to the DBOS or PBOS regimen, especially with regards to cardiovascular, transaminase elevation, or testicular toxicity is low.

3.2.1.1.1. Toxicology

In preclinical toxicology studies in dogs, increases in CK, ALT, AST, lactate dehydrogenase, and potassium were observed in the 4-week toxicity study at the highest dose (2000 mg/kg/day). Increases in total cholesterol and phospholipids were also observed in the 4- and 13-week toxicity studies at doses of 100 mg/kg/day and higher. In the 4-week toxicity study, slight prolongation of QT interval and QTc was observed at Week 4 in both sexes at 2000 mg/kg/day. However, no prolongation of QT interval and QTc was noted in the 13-week toxicity study in either sex at up to 100 mg/kg. In 4- and 13-week repeated-dose oral toxicity studies in dogs, decreased body weight or suppressed body weight gain, or both, and decreased food consumption were observed. In blood biochemistry, changes in CK, lactate dehydrogenase, ALT, AST, total cholesterol, phospholipids, $\alpha_1$globulin content and ratio, potassium, and myoglobin were observed. In electrocardiography, a slight prolongation of QT interval and QTc was observed only at the highest dose in the 4-week repeated-dose oral toxicity study. In histopathological examination, changes in the muscle fibers were observed. Stress-related changes secondary to body weight loss were observed in the thymus and adrenal grand. These changes showed reversibility or a tendency for reversibility.

3.2.1.2. Clinical

In the first part of a multi-stage, 14-day EBA trial in participants with pulmonary DS-TB, OPC-167832 demonstrated an average decline of 1.10, 1.93, 2.23, and 2.08 $\log_{10}$ colony forming units (CFU) in sputum specimens obtained from participants administered 3, 10, 30, and 90 mg daily for 14 days, respectively, compared with a 2.69 $\log_{10}$ CFU decline in participants receiving HRZE (Dawson et al, 2021; www.clinicaltrials.gov, NCT03678688). No serious or significant AEs were observed at these doses. Single oral doses up to 480 mg OPC-167832 were well-tolerated in a previous Phase 1 trial in healthy volunteers; there were no serious or severe AEs and no participants were discontinued from the trial due to an AE (Study 323-201-00001). Mild transaminase elevations were noted in approximately 20% of subjects receiving OPC-167832 although the frequency and severity of the elevations were not significantly different than placebo. Although slight QT prolongation was noted at the highest doses in two 4-week dog studies, a slight negative correlation was observed between changes in QTcF from baseline and placebo, and OPC-167832 plasma concentrations. The combination of delamanid, bedaquiline and OPC-167832 was first evaluated in the second part of the 14-day EBA trial; the combination exhibited similar early bactericidal activity to HRZE supporting further evaluation for longer term treatment (Dawson et al, 2023b). This combination is currently ongoing assessment in a longer-term (4 months) treatment trial with results anticipated by 2025 (www.clinicaltrials.gov, NCT05221502; see Section 3.3.1.2 for more details).

See Section 3.2.3 for discussion of potential for drug-drug interactions with OPC-167832.

Because of OPC-167832's high bactericidal activity, low frequency of spontaneous resistance mutations, and novel mechanism of action, its inclusion in a regimen may increase the barrier to resistance in a combination regimen (Otsuka OPC-167832 Investigator Brochure, 2024).

3.2.2. Sutezolid

Sutezolid is a novel oxazolidinone antibiotic that inhibits growth of Mtb by binding to the bacterial 50S ribosome and blocking microbial translation and protein synthesis. As described in Section

2.1, in a clinical trial of refractory XDR-TB patients, linezolid, a member of the oxazolidinone class with potent activity against TB, has demonstrated robust efficacy as monotherapy for XDR-TB patients with chronic severe disease (Lee et al, 2012; Lee et al, 2015) and was approved by the FDA as a key component of the BPaL regimen (bedaquiline, pretomanid, and linezolid) for the treatment of TI/NR MDR-TB and XDR-TB based on the results of the Nix-TB trial (Conradie et al, 2020). However, linezolid is associated with significant side-effects, including myelosuppression and neuropathy that are dose- and duration-related (see Section 3.2.2.2.1). Currently in Phase 2 development, sutezolid holds promise as a safer alternative to linezolid for treatment of TB.

3.2.2.1. Nonclinical

Sutezolid is a thiomorpholine analog of linezolid with similar potency in vitro toward DS- and MDR-TB but improved bactericidal activity in mouse models of TB including increased sterilizing activity over linezolid in combination with bedaquiline and pretomanid. Nonclinical studies have demonstrated that, for successful treatment of pulmonary TB, drugs need to penetrate complex lung lesions and permeate the caseum cavity to demonstrate their activity against slowly replicating or nonreplicating bacilli in the caseous milieu of lesions. An ex-vivo caseum assay study (Subbian et al, 2011) was conducted to assess the potency of linezolid and sutezolid against slowly replicating or nonreplicating bacilli in their native caseous environment. The linezolid concentration required to reduce bacterial load by one log was 128 μM, whereas sutezolid concentration to do the same was 8 μM, and sutezolid M1 metabolite was 50 μM. Sutezolid (together with its M1 metabolite) appears to be more potent with respect to caseum-cidal activity compared to linezolid, based on ex-vivo assay data.

3.2.2.1.1. Toxicology

The toxicology risk assessment for sutezolid was integrated from studies conducted by multiple Sponsors including Global TB Alliance (28-Day study in rats or monkeys, GLP), National Institutes of Allergy and Infectious Diseases (6-month study in rats, GLP) and Bill & Melinda Gates Medical Research Institute (26-week study in rats and 17-week [4-month] study in monkeys, GLP; Embryo-fetal development studies, non-GLP and GLP; pre- and post-natal development study, GLP). As a novel agent in consideration for addition to the DBOS or PBOS regimens included in this study, the following key areas were assessed based on known liabilities for linezolid, bedaquiline, delamanid, and pretomanid.

- *Hematopoietic toxicity:* Reversible effects on the hematopoietic system was observed at high doses in studies of 28-days in duration but were absent at all doses in studies of longer duration in rats (6-months) and monkeys (4-months). Adequate safety multiples for sutezolid have been established for effects on the hematopoietic system suggesting a low risk for hematopoietic toxicity in humans (Sutezolid Investigator Brochure, 2023).
- *Cardiovascular toxicity:* Sutezolid has no risk for cardiovascular toxicity based on functional assessment in monkeys and humans (Phase 1 studies), and microscopic evaluation of the heart in nonclinical studies up to 6-months in duration. Risk for an additive or synergistic cardiovascular toxicity by sutezolid to bedaquiline or delamanid in the DBOS or PBOS regimen is low.

- *Elevated transaminases:* Drug-mediated effects on liver or skeletal muscle can result in elevation of transaminases (ALT and/or AST) and increases in bilirubin provides specific diagnoses of liver injury. In a 6-month rat study, sutezolid caused a reversible increase in AST levels that was associated with skeletal muscle degeneration and isolated mononuclear cell infiltrate. These findings were not considered adverse because of low severity affecting isolated myofibers with evidence of regeneration. There were no elevations in transaminases in a 4-month monkey study at higher exposures than in rats. A transient increase in ALT by sutezolid, without elevation of bilirubin, was observed in a Phase 2a trial, but not in a MAD trial, both of 14 days duration. Addition of sutezolid in a PBOS or DBOS trial may lead to an additive increase to previously observed elevated transaminases by bedaquiline, pretomanid, or delamanid, and clinical monitoring to differentiate transaminase elevation from liver or skeletal muscle will be implemented in DBOS and PBOS regimens.
- *Reproductive Toxicity:* Embryo-fetal development (EFD) studies with sutezolid have been conducted in the mouse, rat, and rabbit. In a definitive study in rats, sutezolid caused maternal toxicity, characterized by significant lowering of food consumption that was acute in onset, and developmental toxicity, characterized by minimal embryo/fetal survival and a low incidence of retinal malformation. Sutezolid caused severe maternal toxicity in rabbits, characterized by severe feed restriction at subtherapeutic doses; the rabbit was considered an unsuitable species for conduct of a definitive EFD study and mice was selected as the second species for a definitive pEFD study. Sutezolid did not cause maternal or developmental toxicity in mice at up to the limit dose of 1000 mg/kg/day. The NOAEL for both maternal and EFD toxicity in mice provided safety multiples of 13-fold to sutezolid; the NOAEL for both maternal and embryo-fetal developmental toxicity in pregnant rats provided safety multiples of ~4-fold to sutezolid. These definitive developmental and reproductive toxicology studies support use of sutezolid in clinical studies enrolling women of child-bearing potential. In a fertility and early embryonic development study, sutezolid had no effect on fertility in either sex or on early embryonic development in females at any dose tested up to safety multiples of ~4-fold in males or females. In the pre- and post-natal development study, there was a dose-dependent increased incidence in pup mortality at safety multiples of ≥ 1-fold to sutezolid in the absence of maternal toxicity. No abnormalities were identified following neurobehavioral assessment or in reproductive performance in surviving pups in the F1 generation at the NOAEL dose of 30 mg/kg/day. Addition of sutezolid in a PBOS or DBOS regimen will not have any additional reproductive potential risk. The new findings of perinatal pup losses with sutezolid should not preclude the inclusion of females of childbearing potential in a clinical trial with an informed consent that includes precautions to guard against pregnancy, and exclusion criteria for pregnancy or breastfeeding.

Although well-tolerated, sutezolid suppressed appetite in rats, and albeit this may be a rodent-specific effect, appetite suppression in humans should be monitored. Sutezolid inhibited human monoamine oxidase (MAO) isoforms A and B, and its major metabolite inhibited MAO-B, all at concentrations that would be relevant in humans at a dose of 1200 mg. This inhibition could impact disposition of dietary tyramine, and interaction with serotonergic antidepressants is possible.

Overall, sutezolid has an improved safety profile compared to linezolid in nonclinical toxicology studies in rats and monkeys up to 4 or 6-months in duration. The toxicology package supports dosing of up to 4-months in humans. An additive elevation of transaminases of skeletal muscle origin may occur from treatment with the PBOS or DBOS regimen. Clinical monitoring that can differentiate transaminase elevation of liver or skeletal muscle origin will be performed.

3.2.2.2. Clinical

Sutezolid has been studied in a single and multiple ascending dose (MAD) trial in healthy volunteers, in a 14-day EBA trial in TB patients, and in a Phase 2b dose-ranging trial in combination with bedaquiline, delamanid, and moxifloxacin for 4 months (Wallis et al, 2010; Wallis et al, 2011; Wallis et al, 2014; Heinrich et al, 2023). Sutezolid could not be excluded as a possible cause of colitis in one MAD trial participant who had to discontinue sutezolid (Wallis et al, 2014; Clinical Study Report for Study B1171003). In the EBA trial, with both doses evaluated (600 mg BID and 1200 mg QD), sutezolid demonstrated similar substantive bactericidal activity in the sputum of patients over the 14-day treatment period (Wallis et al, 2014; Clinical Study Report for Study B1171003); no serious TEAEs, premature discontinuations, or dose reductions due to laboratory abnormalities occurred, and no effect on the QT interval duration was observed. Although generally well-tolerated, gastrointestinal AEs were observed. However, among the 50 sutezolid-treated patients randomized in the trial, 7 (14%) (4 on 600 mg BID and 3 on 1200 mg QD) had transient, asymptomatic ALT elevations (>3-fold upper limit of normal) on Day 14 that subsequently normalized during the follow up period of the trial; none met Hy's criteria for serious liver injury. In an open-label, randomized, controlled trial assessing the safety and efficacy of a range of sutezolid doses (600 mg QD, 600 mg BID, 800 mg BID and 1200 mg QD) administered over 12 weeks to patients with pulmonary DS-TB in combination with bedaquiline, delamanid, and moxifloxacin, the combination was well tolerated with no neuropathy nor myelosuppression identified (except one case of neutropenia with a possible alternative cause). Additionally, there was only participant with hepatotoxicity requiring treatment interruption observed although treatment was successfully reintroduced. However, there was no clear dose-effect on slope of MGIT TTP over 12 weeks for sutezolid which may have been due to a limitation in trial design (Heinrich et al, 2023).

The clinical data to date, independent of the expanding preclinical evidence base, has not identified any significant safety concerns that would preclude further clinical development of sutezolid for TB treatment. However, this conclusion is limited by the small number of subjects who have received the drug in the anticipated dosing range and duration needed for treatment. Therefore, close monitoring with frequent assessments of patients in the planned Phase 2b/2c regimen trial is required and the 2-stage design has been incorporated to further mitigate risk.

Although no human studies have been conducted to evaluate the potential PK drug-based interaction of sutezolid or its metabolites with other drugs, extrapolation from in vitro data for the other drugs in the DBOS and PBOS regimens suggest that the potential for drug interaction is low. No significant inhibitory or inductive effect by sutezolid or its metabolites was observed on relevant cytochrome P450 enzymes. Based on sutezolid's inhibition of MAO, which increases levels of the neurotransmitter serotonin, potential participants for this trial requiring concomitant use of medications or herbal products that may also increase serotonin levels, such as MAO inhibitor and selective serotonin reuptake inhibitor antidepressants, will not be eligible to minimize

the potential risk of serotonin syndrome (see Appendix 1, Section 13.1). See Section 3.2.3 for additional discussion of potential for drug-drug interactions with sutezolid.

3.2.2.2.1. Potential Oxazolidinone Class Effects

Close monitoring of potential safety concerns is indicated in the trial given the limited number of participants exposed to longer dosing with sutezolid in combination with other drugs. Although linezolid will not form part of the regimen, its AE profile is important to appreciate for the toxicity it demonstrated both with longer term use as monotherapy and as part of the BPaL regimen and to ensure appropriate monitoring of potential class effects that might occur with sutezolid as a related compound. (Lee et al, 2012; Conradie et al, 2020; Conradie et al, 2022.). In a clinical setting, AEs associated with linezolid in patients with TB include neurotoxicity (ie, peripheral neuropathy and optic neuritis), myelosuppression, hyperlactatemia, and diarrhea, all of which are presumably secondary to the inhibition of mitochondrial protein synthesis (MPS) (Nahid et al, 2019). A published systematic review of 12 studies conducted in 11 countries globally reported an AE rate of 58.9% among patients treated with linezolid (hematological, neurological, and gastrointestinal), predominantly noted in individuals treated with a dosages ≥600 mg/d (Lifan et al, 2019; Agyeman et al, 2016). Onset of hematological toxicity by linezolid is sub-acute, often after only 2 to 3 weeks of treatment, and can involve any cell line. A study by Song et al (2015) examining a correlation between mitochondrial function in blood, linezolid blood concentrations (C_{min}), and adverse events concluded that myelosuppression and neuropathy were secondary to mitochondrial toxicity and correlated with trough concentrations of linezolid. Although inhibition of MPS by sutezolid (12.5 μM) is generally similar to linezolid (8 to 13 μM) (Sutezolid Investigator Brochure, 2023), peak plasma concentrations of linezolid (~12.7 μg/mL; Linezolid [Zyvox®] Product Label, 2021) is significantly higher compared to sutezolid (~1.97 μg/mL; Wallis et al, 2014) at doses of 600 mg or 1200 mg QD, respectively, suggesting a potential for differentiation in therapeutic index for MPS inhibition for sutezolid compared to linezolid and possibly improved safety profile.

Based on nonclinical data in rats/monkeys and clinical data from Phase 1 and 2 studies where there were no findings of myelosuppression, sutezolid is expected to have a more favorable safety profile than linezolid.

3.2.3. Potential Drug-Drug Interactions for Each Agent Comprising the Experimental Regimens

Based on a comprehensive review of the metabolizing activity and mechanisms of delamanid pretomanid, sutezolid, bedaquiline and OPC-167832, as well as results from clinical drug-drug interaction (DDI) studies, pertinent information regarding the potential for drug-drug interactions as either perpetrator or victim is summarized for each drug in Table 8.

Table 8 Potential Drug-Drug Interactions for the Anti-TB Agents Comprising the Investigational Treatment Regimens

Drug	DDI as a Perpetrator	DDI as a Victim
Delamanid	• In-vitro studies showed that delamanid did not inhibit CYP450 enzymes • In-vitro studies showed that delamanid and metabolites did not have any effect on the	• Co-administration with rifampicin 300 mg QD, a strong CYP3A4 inducer, reduced delamanid exposure up to 45% in healthy subjects

Drug	DDI as a Perpetrator	DDI as a Victim
	transporters MDR1(p-gp), BCRP, OATP1, OATP3, OCT1, OCT2, OATP1B1, OATP1B3, and BSEP • Co-administration with delamanid increased steady state plasma concentrations of ethambutol by approximately 25% with unknown mechanism. • Delamanid did not affect the exposure of rifampicin, isoniazid, and pyrazinamide • Delamanid did not affect the exposure of tenofovir disoproxil, lopinavir/ritonavir and efavirenz	• Co-administration with efavirenz 600 mg QD, a weak CYP3A4 inducer, did not result in clinically relevant reduction in delamanid exposure
Pretomanid	• Co-administration of pretomanid with midazolam, a CYP3A index substrate, resulted in no clinically significant effect on the exposure of midazolam or its major metabolite, 1'-OH-midazolam • Pretomanid inhibited OAT3 with 66% inhibition observed at 15 µM in vitro; decreased creatinine urinary secretion but unchanged GFR is possibly due to inhibition of OAT3-mediated active secretion • In-vitro studies suggested negligible inhibition of OAT1, OCT1, OATP1B1, MATE1, MATE2-K, P-gp, BCRP, BSEP, OCT2, or OATP1B3 at clinical concentrations • Pretomanid had negligible effect on the PK of co-administered lopinavir, ritonavir, or efavirenz (PMID# 24957823)	• Co-administration with rifampicin 600 mg QD or efavirenz 600 mg QD, CYP3A4 inducers, resulted in a decrease in pretomanid exposure. • Co-administration with lopinavir/ritonavir did not have a clinically relevant effect on pretomanid exposure
Bedaquiline	• In vitro, bedaquiline did not inhibit CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A4/5, and CYP4A • In vitro, bedaquiline did not induce CYP1A2, CYP2C9, CYP2C19, or CYP3A4 activities • In vitro, bedaquiline did not inhibit P-gp, OATP1B1/1B3, OCT1/2, OAT1/3, and MATE-1/2K • In vitro, bedaquiline inhibited BCRP at concentrations achieved in the intestine • Bedaquiline did not affect the exposures of ethambutol, kanamycin, pyrazinamide, ofloxacin and cycloserine • Clinical data in HIV/MDR-TB co-infected patients on the combined use of lopinavir/ritonavir with bedaquiline are not available	• Co-administration with rifampicin 600 mg QD, a strong CYP3A4 inducer, reduced bedaquiline exposure by 52% in healthy subjects • Co-administration with ketoconazole 400 mg QD, a strong CYP3A4 inhibitor, increased bedaquiline exposure by 22% in healthy subjects • Co-administration with isoniazid/pyrazinamide did not result in clinically relevant changes in bedaquiline exposure • Co-administration with Kaletra (400 mg lopinavir + 100 mg ritonavir) BID increased bedaquiline exposure by 22% • Co-administration with nevirapine 200 mg BID did not result in clinically relevant changes in bedaquiline exposure
OPC-167832	• In vitro, OPC-167832 inhibited CYP2C9, CYP2C19, CYP2A6, CYP2B6, CYP2C8, CYP2D6, and CYP3A4; however, inhibition concentrations were not clinically relevant based on the minimum exposure required for	• OPC-167832 is mainly metabolized by CYP3A4/5, thus it is likely to be the victim of a CYP3A inhibitor or inducer

Drug	DDI as a Perpetrator	DDI as a Victim
	maximum therapeutic effect from nonclinical studies • In vitro, OPC-167832 showed time-dependent inhibition for CYP3A4 • In vitro, OPC-167832 showed an induction potential for CYP3A4 • In vitro, OPC-167832 inhibited P-gp and BCRP at concentration achieved in the intestine	
Sutezolid	• In vitro, sutezolid and its active metabolite (PNU-101603) did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 • In vitro, sutezolid and PNU-101603 did not induce CYP1A2, 2B6, and CYP3A4 • In vitro, sutezolid inhibited 50% MAO-B activity at 1.7 μM; inhibition of MAO-A and B is possible at the efficacious concentrations of sutezolid and PNU-101603 • In vitro, sutezolid inhibited BCRP intestinal and hepatic efflux pump and OAT3 renal uptake transporter	• In HLM incubation, ketoconazole, a selective CYP3A4 inhibitor, inhibited sutezolid metabolism by 33% • In HLM incubation, inhibition of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 had no effect on sutezolid metabolism • In vitro, inactivation of FMOs decreased sutezolid metabolism by 20% • In vitro, sutezolid and PNU-101603 are substrates of BCRP intestinal and hepatic efflux pump and PNU-101603 is a substrate of OAT3 renal uptake transporter

PK drug-drug interactions between components of the proposed regimens featured in Section 3.3.1 (DBOS) and Section 3.3.2 (PBOS) and common co-administered medications (such as anti-retroviral drugs and oral contraceptives) will be monitored for DBOS and PBOS agents only during the trial.

Information regarding the PK drug-drug interactions for drugs that are already approved and are part of the proposed regimen (delamanid, pretomanid, and bedaquiline) is available. Bedaquiline and pretomanid are metabolized by CYP3A4 and are therefore susceptible to induction/inhibition of this enzyme. Co-administration of strong and moderate CYP3A4 inhibitors/inducers should be avoided. Some commonly co-administered ART (eg, lopinavir, ritonavir, and efavirenz) and oral contraceptives are also impacted by the CYP3A4 metabolic pathway and will not be permitted for randomized participants (see Section 7.5.1.1.1).

In patients treated with bedaquiline, systemic exposure was found to be lower in patients of African or African American origin than in patients from other race categories. No dose adjustment is planned for patients of African or African American origins since in previous clinical studies this lower exposure was not considered to be clinically relevant.

Sutezolid and OPC-167832 are investigational drugs and limited information is available regarding their potential for clinical PK drug-drug interactions. A Phase 2a 14-day evaluation of the EBA of OPC-167832 in combination with bedaquiline and delamanid completed in 2022 demonstrated no apparent clinically significant PK drug-drug interactions for the combination (OPC-167832 Investigator's Brochure, 2024; Dawson et al, 2023b). Inhibition of MAO-A and B is possible at the efficacious concentrations of sutezolid and its metabolite PNU-101603. Therefore, sutezolid

has the potential for interaction with adrenergic and serotonergic agents and those should be avoided (similar to what is suggested in the linezolid label).

Standard of care for DS-TB (2HRZE/4HR) will be initiated for participants in the experimental arms for whom Investigators have determined treatment cannot be stopped at the end of assigned treatment duration, for whom trial treatment was permanently discontinued prior to the end of the assigned treatment duration, and for participants who developed a TB relapse episode during the post-treatment follow-up period (if confirmed to be DS-TB). These participants randomized to experimental arms who are later placed on SOC will have some exposure to the experimental drugs depending on their elimination half-life, particularly delamanid and bedaquiline.

Delamanid and its metabolite, DM-6705, have long half-lives (30 to 38 hours and 121 to 322 hours respectively). However, delamanid and its metabolites have low potential for PK drug-drug interactions with the 2HRZE/4HR regimen (Table 8; Deltyba™ Summary of Product Characteristics, 2023).

The mean terminal elimination half-life of bedaquiline and the N-monodesmethyl metabolite (M2) is approximately 5.5 months. In vitro bedaquiline is not an inhibitor or an inducer of most of the CYP enzymes and of the P-gp transporter. Therefore, bedaquiline has a low potential for PK drug-drug interactions (as a perpetrator) with the 2HRZE/4HR regimen (Table 8). Rifampicin will increase the clearance of bedaquiline, but this is not clinically relevant for participants that have already failed one of the experimental regimens as bedaquiline would not be considered an active anti-TB drug once they are placed on 2HRZE/4HR.

The mean half-life of pretomanid is approximately 17 hours. Pretomanid is not an inhibitor or an inducer of most of the CYP enzymes. Therefore, pretomanid has a low potential for PK drug-drug interactions (as a perpetrator) with the 2HRZE/4HR regimen (Table 8).

Sutezolid and its active metabolite PNU-101603 have a short plasma half-life of 2 to 4 hours. Sutezolid and PNU-101603 are not inhibitors or inducers of most of the CYP enzymes (Table 8). Therefore, there is a low potential for PK drug-drug interactions (as a perpetrator) with the 2HRZE/4HR regimen.

OPC-167832 plasma half-life is approximately 16 hours. In vitro data suggest that OPC-167832 is not an inhibitor of the major CYP enzymes at the expected therapeutic exposure. However, OPC-167832 showed an induction potential for CYP3A4. However, since OPC-167832 will be mostly eliminated approximately 2 to 3 days post dose there is a low potential for a clinically significant PK drug-drug interaction (as a perpetrator) with the 2HRZE/4HR regimen.

Sparse PK samples of all drugs (and relevant metabolites) in the experimental regimens will be obtained from participants during the trial and exposure to the various drugs will be monitored. PK assays will also be performed for key antiretrovirals (eg, dolutegravir). To mitigate the risk of PK drug-drug interaction, the IDMC may review the available PK data during regular scheduled safety review meetings and specified interim analyses for safety and efficacy assessments.

3.3. Combination Product Regimens

Two novel regimens will be studied, namely PBOS and DBOS. Although there is no prior clinical experience with either regimen, the clinical experience with combinations of some of the drugs in these regimens provides insight into the potential toxicities of the regimen, including the overlapping toxicities of the component drugs for which careful monitoring is indicated.

3.3.1. Delamanid, Bedaquiline, OPC-167832 and Sutezolid (DBOS)

3.3.1.1. Supportive Evidence From Combination Evaluation: Delamanid and Bedaquiline

3.3.1.1.1. Efficacy

The DELIBERATE trial (www.clinicaltrials.gov; NCT02583048) conducted to evaluate potential effects on cardiac conduction from combined administration of delamanid and bedaquiline is the only randomized, controlled trial published to date that provides controlled data on the impact of the combined use of delamanid and bedaquiline on sputum culture conversion (Dooley et al, 2021). In this trial, among 82 participants with MDR-TB who initiated treatment (including 31 in total with HIV), cumulative SCC was:

- by Week 8 – delamanid + background regimen, 20/24 (83%; 95% confidence interval [CI]: 65-95); bedaquiline + background regimen, 21/24 (88%, CI: 71-97); and delamanid + bedaquiline + background regimen, 19/20 (95%; CI: 79-100)
- by Week 24 – delamanid + background regimen, 91% (CI: 76-99), bedaquiline + background regimen, 92% (77 to 99); and delamanid + bedaquiline + background regimen, 95% (79 to 100)

Additionally, the "end TB" prospective observational cohort study provides strong supportive evidence for the potential benefit of combining delamanid with bedaquiline for treatment (Franke et al, 2021). This study was conducted to assess the use of delamanid and bedaquiline in MDR-TB treatment in real world conditions, including among patients with higher risk for unfavorable treatment outcomes (eg, HIV and/or hepatitis C virus coinfection, diabetes mellitus, and/or XDR-TB - patients often excluded from clinical study). Encouraging results were observed; among 1109 patients with baseline sputum cultures positive for MDR-TB enrolled in 17 countries across Asia, Africa, and Latin America, 939 (85%) experienced sputum culture conversion within 6 months of initiating treatment (Franke et al, 2021). In terms of treatment, 696 (63%) received multidrug treatment including bedaquiline, 303 (27%) including delamanid, and 110 (10%) including both; overall, 911 (82%) received treatment including linezolid.

Additional publications reporting on cohorts of patients that have received combination bedaquiline and delamanid generally demonstrate good efficacy in terms of faster sputum culture conversion than historical cohorts and favorable treatment outcomes (Ferlazzo et al, 2018; Mohr et al, 2019; Sarin et al, 2019; Hafkin et al, 2019; Kwon et al, 2021; Olayanju et al, 2018; Das et al, 2020). Mortality remains significant but should be interpreted in the context that, to date, bedaquiline and delamanid have primarily only been given together for patients with extensive drug resistance and/or advanced TB disease with few other treatment options. Many of these patients that received combination bedaquiline and delamanid therapy were also given linezolid

but, unfortunately, efficacy outcomes were not reported separately for individuals that received all three drugs.

3.3.1.1.2. Safety

Concomitant use of bedaquiline and delamanid was previously not recommended by the WHO until the 2020 update of the MDR-TB guidelines due to concerns for potential synergistic cardiotoxicity. However, safety results from the aforementioned DELIBERATE trial demonstrated that combining bedaquiline and delamanid has a modest, no more than additive, effect on the QTc interval, and supports the use of these agents together in patients with normal baseline QTc values. Specifically, individuals receiving delamanid and bedaquiline for 24 weeks in addition to a multidrug background regimen experienced a mean increase of 20.7 ms in QTcF duration compared to a 12.3 ms increase in the bedaquiline-only arm and an 8.6 ms increase in the delamanid-only arm. Grade 1 or 2 QTcF prolongation AEs occurred in 44%, 36%, and 41% of participants in each respective arm. Importantly, there were no Grade 3 or 4 QTcF prolongation AEs, no treatment interruptions due to QTcF prolongation, and no deaths during trial treatment. Only 2.7% of DELIBERATE trial participants received the combination of bedaquiline, delamanid, and linezolid (Dooley et al, 2021). Findings from the DELIBERATE trial and multiple observational studies have provided sufficient evidence (Ferlazzo et al, 2018; Mohr et al, 2018; Borisov et al, 2019; Mohr et al, 2019; Sarin et al, 2019; Hafkin et al, 2019; Kwon et al, 2021; Olayanju et al, 2018; Das et al, 2020) for WHO to state that, from a safety perspective, bedaquiline and delamanid can be used together for MDR-TB patients with limited options for forming a DR-TB regimen of sufficient strength (WHO, 2022). Although linezolid was frequently given along with bedaquiline and delamanid in these cohorts, none of the publications report adverse event data separately for individuals that received all three drugs.

3.3.1.2. Supportive Evidence From Combination Evaluation: Delamanid, Bedaquiline and OPC-167832

As outlined in Section 3.2.1, Otsuka Pharmaceuticals has evaluated the early bactericidal activity of OPC-167832 of varying doses over 14-days in stage one of a two-stage trial (www.clinicaltrials.gov; NCT03678688). This trial has progressed to stage two with an evaluation of 14 days of administration of OPC-167832 in combination with delamanid, with bedaquiline, and with delamanid plus bedaquiline currently underway; the trial has completed with results expected to be available in early 2023. Of note, the doses being assessed are OPC-167832 at 30 mg daily, delamanid at 300 mg daily (one of the single daily doses evaluated in the delamanid early bactericidal activity trial referenced in Section 3.1.2 (Diacon et al, 2014) and bedaquiline at 400 mg daily. As reported for Stage 1 in the evaluation of multiple doses of OPC-167832, no serious or severe AEs occurred and no participants were discontinued from the trial due to an AE. A follow-on Phase 2b trial sponsored by Otsuka Pharmaceuticals evaluating OPC-167832 administered as 10 mg, 30 mg, or 90 mg daily in combination with bedaquiline and delamanid for 4 months in patients with DS-TB has completed enrollment in South Africa and is still ongoing with results anticipated by 2025 (www.clinicaltrials.gov; NCT05221502).

3.3.1.3. Dose Selection and Rationale for DBOS Combination Agents

Table 9 outlines the dose and schedule for the combination agents included in DBOS to be used in the Phase 2b/c trial. The justification and rationale for the doses and schedule selected for each of the agents (delamanid, bedaquiline, OPC-167832, and sutezolid) are provided herein.

Table 9 DBOS Regimen Components Dosing and Schedule

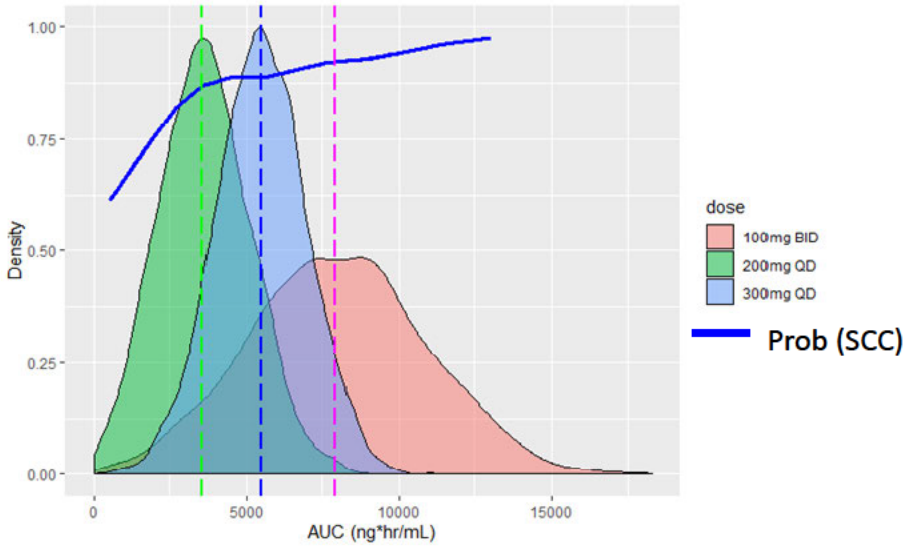
Regimen components	D	B	O	S
Dose and Schedule	300 mg QD for treatment duration	400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment weeks	30 mg QD for treatment duration	1200 mg QD for treatment duration

3.3.1.3.1. Delamanid Dose Selection and Justification

As indicated in the summary of product characteristics for delamanid (Deltyba® SmPC, 2023), the recommended dose for treatment of MDR-TB is 100 mg BID. However, the future utility of a promising pan-TB regimen of shorter treatment duration than required for 2HRZE/4HR will depend in part on the ability to dose once daily. Given past experience from the EBA study of delamanid in which 300 mg administered once daily demonstrated the most robust activity (See Section 3.1.2) and building from results of a generalized model developed by Otsuka based on data from a Phase 3 clinical trial (Von Groote-Bidlingmaier et al, 2019) to correlate sputum culture conversion in MDR-TB patients as a function of daily $AUC_{0\text{-}24hrs}$, use of 300 mg once daily dose for delamanid in the evaluation of the DBOS regimen is supported.

Distribution of $AUC_{0\text{-}24}$ drug concentrations at steady state following 100 mg BID, 200 mg QD and 300 mg QD doses were used to derive the respective distributions of probability of SCC at each of these doses (Liu et al, 2018; Mallikaarjun et al, 2020) Additionally, the degree of QT prolongation from 300 mg QD is expected to be lower than 100 mg BID because exposures for the DM-6705 metabolite of delamanid, which is associated with the QT prolonging effect of the drug, are lower with 300 mg QD than 100 mg BID (Figure 3). The derived SCC distribution at the 300 mg QD dose (M: 0.89, CI: 0.84-0.92) more closely matches the SCC distribution at 100 mg BID (M: 0.91, CI: 0.84-0.97) in comparison to the 200 mg QD dose (M: 0.83, CI: 0.67-0.9). This analysis supports the use of 300 mg QD dose for delamanid in the DBOS regimen, enabling QD administration (instead of BID) while closely matching the SCC performance of the 100 mg BID dose.

Figure 3 Delamanid AUC_{0-24} Distributions at Steady State Versus Probability Of SCC



The shaded area represents simulation of 5000 individual predicted AUC of the delamanid exposure based on the PK data from multiple clinical studies conducted to support the development of delamanid (Diacon et al, 2011; Gler et al, 2012; Von Groote-Bidlingmaier et al, 2019). The blue line represents the probability of achieving SCC.

Delamanid is recommended to be taken with food per its Product Label (Deltyba™ SmPC, 2023).

3.3.1.3.2. Bedaquiline Dose Selection and Rationale

Based on the amalgam of clinical trial and real-world experience with treatment of both DS-TB and MDR-TB patients, bedaquiline will be administered as per the Product Label - 400 mg QD for 2 weeks, then 200 mg thrice weekly for the remaining weeks of treatment (Sirturo® Product Label, 2023). Bedaquiline is recommended to be taken with food per its Product Label.

3.3.1.3.3. OPC-167832 Dose Selection and Rationale

Based on a nonclinical infection model in mice, the minimum AUC value to achieve maximum efficacy should be greater than 2252 ng·h/mL. The observed median steady state AUC exposure in the MAD trial 003 Stage 1 following 14-day administration of 30 mg of OPC-167832 was above this threshold (2464 ng·h/mL; 37% CV; preliminary results). Significant EBA effect (change in TB bacterial load in sputum) was observed in TB patients in this stage: the median results were comparable at the 10, 30, and 90 mg OPC-167832 dose levels, suggesting that the required efficacy threshold in humans may be lower as compared to the threshold that was estimated in an animal model.

The overall aim of this trial is to estimate the shortest XBOS regimen duration capable of delivering comparable efficacy and safety to the 6-month standard regimen. Although there is inherent uncertainty in translating non-clinical and EBA results to durable cure in patients, OPC-167832 will be evaluated at 30 mg QD based on the totality of nonclinical and clinical data

currently available. Regimen shortening is likely contingent upon achieving and sustaining effective exposures across heterogeneous sites of infection such as caseous lesions, which may not be clearly discernable in the 14-day EBA response. By way of example, pretomanid was studied at doses ranging from 50 mg to 1200 mg QD in two 14-day EBA studies (Diacon et al, 2010; Diacon et al, 2012a). These data suggest that 100 and 200 mg QD had no discernable difference in monotherapy EBA effects, yet the 200 mg arm appeared to provide improved favorable status (75%) relative to the 100 mg arm (67%) in the STAND trial assessing treatment shortening potential of regimens containing pretomanid (Tweed et al, 2021). Further, no safety or tolerability issues were observed in the 14-day OPC-167832 EBA trial that would preclude the continued evaluation of 30 mg. Toxicology studies support the clinical evaluation of exposures up to 51,000 ng*hr/mL, which is 20-fold higher than exposures expected with a 30 mg QD dose. Taken together, the evaluation of 30 mg is expected to optimize the balance of contributing towards maximum cure within a safe and well-tolerated exposure range.

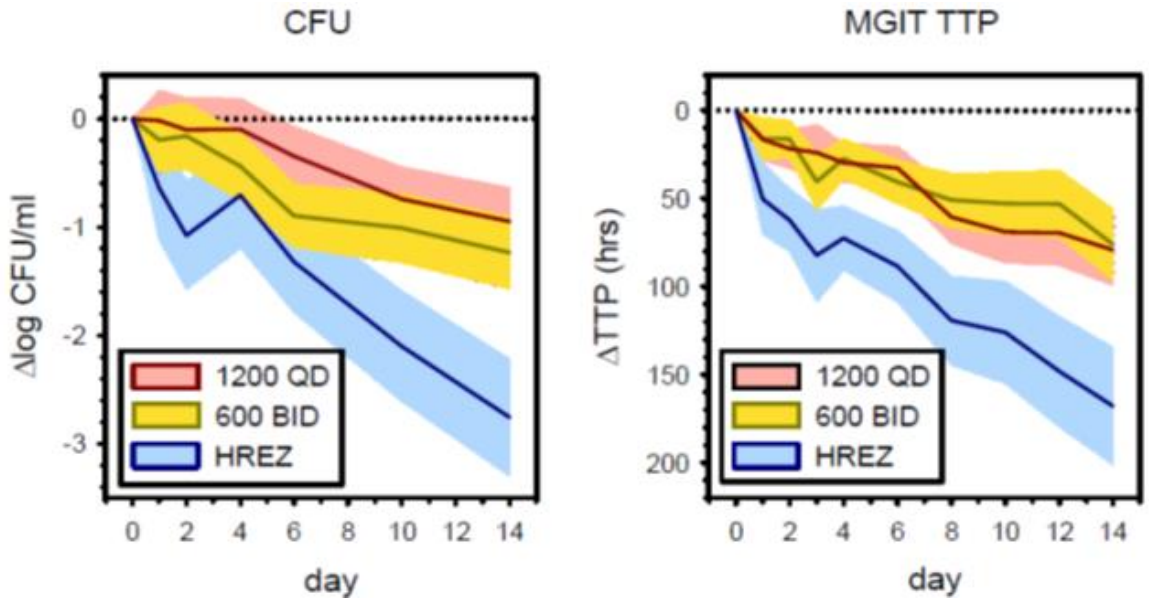
As previously noted, a separate Phase 2b/c trial evaluating OPC-167832 administered at 10 mg QD, 30 mg QD, or 90 mg QD in combination with delamanid 300 mg QD and bedaquiline 400 mg QD for 2 weeks then 200 mg thrice weekly for 17 weeks total has completed enrollment but is still ongoing (www.clinicaltrials.gov; NCT05221502). Available findings from that trial regarding the optimal dose of OPC-167832 will be reviewed to determine if the dose of OPC-167832 should be modified in Stage 2.

Median OPC-167832 exposures and peak concentrations were higher (19% and 44%, respectively) when administered after a standard meal compared to the fasting state in a crossover single dose trial in healthy volunteers (OPC-167832 Investigator's Brochure, 2024). Based on this finding, OPC-167832 should be administered with food in this trial.

3.3.1.3.4. Sutezolid Dose Selection and Rationale

Sutezolid was evaluated at 1200 mg QD and 600 mg BD in its EBA evaluation trial (Wallis et al, 2014). Both dosing schedules resulted in changes in sputum $\log_{10}$ CFU over the entire period of treatment that excluded zero. Separate analysis of Days 0 to 2 and 2 to 14 showed the effect was significant only during the later interval. A trend toward a superior effect was apparent in the mean values across days when sutezolid was given as 600 mg BID, but the confidence intervals for the 2 dosing schedules largely overlapped (Figure 4). As previously noted, (Section 3.2.2.2), during the monotherapy EBA trial for sutezolid, 14% of patients receiving sutezolid experienced transient, asymptomatic ALT elevations that subsequently returned to normal.

Figure 4 Daily CFU and MGIT TTP Counts Following Sutezolid Administration



Shading indicates 90% CI. A trend toward reduced activity was noted in CFU counts with daily dosing, but no effect was apparent on MGIT TTP.

Low dose linezolid regimens (300 mg BID and 300 mg QD) have been reported effective for longer term treatment of Mtb (Lee et al, 2012; Lee et al, 2015). A recent meta-analysis of 23 studies involving 507 patients did not reveal a strong difference between linezolid doses (<and> 600mg QD) on efficacy against MDR Mtb; although there was some evidence for lower doses being less effective (Agyeman et al, 2016). These observations suggest that in longer-term treatment with linezolid, doses of 1200 mg QD and 600 mg BID may have comparable efficacy against MTB.

In addition, in the linezolid EBA trial that investigated 600 mg BID and QD doses (Dietze et al, 2008), a linezolid dose of 300 mg QD (which has been reported effective for longer term treatment of Mtb above) may struggle to demonstrate EBA activity, at least over 7 days.

Based on the linezolid experience described above it appears that a 14-day EBA assessment is too short to fully characterize the long-term anti-TB effect of oxazolidinone. Therefore, a 1 log CFU reduction over 14 days with sutezolid 1200 mg QD in the monotherapy EBA trial (Wallis et al, 2014) likely underestimates its long-term anti-TB effect. These efficacy findings along with safety and toxicology data support further development of sutezolid 1200 mg QD as a component of new tuberculosis regimens. Though a more recently completed open-label, randomized, controlled trial assessing the safety and efficacy of a range of sutezolid doses (600 mg QD, 600 mg BID, 800 mg BID and 1200 mg QD) administered over 12 weeks to patients with pulmonary DS-TB in combination with bedaquiline, delamanid, and moxifloxacin demonstrated no clear dose-effect on slope of TTP from sputum cultures likely due to trial design limitations, the combination with all doses of sutezolid evaluated was well tolerated including no neuropathy nor myelosuppression identified (except one case of neutropenia with a possible alternative cause) (Heinrich et al, 2023).

There were no apparent food effects on the pharmacokinetics of sutezolid in the 14-day Phase 1 multiple ascending dose trial in healthy volunteers (Pfizer. PNU-100480 Clinical Study Report, Protocol B1171002 [2011] [on file]). Sutezolid should be administered with food in this trial.

3.3.1.4. Summary for DBOS

The totality of the available non-clinical evidence demonstrating the substantial decrease in time to durable cure in the relapsing mouse TB model and decreased time to extinction in the hollow fiber system with the DBOS 4-drug combination regimen relative to the control regimen (see Section 2.1.1), as well as the compelling improvement in SCC and outcomes associated with use of delamanid and bedaquiline separately leading to their respective registration and in combination together in the context of a broader real world population of MDR-TB patients supports moving forward with evaluation of DBOS for treatment shortening potential in this trial (Gler et al, 2012; Diacon et al, 2014; Franke et al, 2021). Although the experience with both agents in the context of treating DS-TB is more limited, the EBA trial results for delamanid demonstrating the greatest activity with the 300 mg dose in DS-TB patients (Diacon et al, 2011) and similar experience gained with the bedaquiline EBA trial across a range of doses in DS-TB (Diacon et al, 2013) add compelling support for evaluation of the regimen for "pan-TB" treatment. Likewise, the results from the 14-day EBA trial for OPC-167832 (OPC-167832 Investigator's Brochure, 2024; www.clinicaltrials.gov, NCT03678688) and sutezolid (Wallis et al, 2014) have demonstrated substantive early activity of these agents in DS-TB patients and supports the potential for additive effect in combination with delamanid and bedaquiline.

From the standpoint of safety, though the DBOS regimen has not been tested previously in the clinic, the safety of combining delamanid and bedaquiline for longer-term treatment (up to 6 months) has been rigorously evaluated in the DELIBERATE trial and the combined effect of the two agents on QTc prolongation has been well characterized (Dooley et al, 2021). The results support their use in this trial with close monitoring. Although there is limited data on OPC-167832 and sutezolid when administered for longer than 2 weeks and/or in combination with other anti-TB agents, the favorable safety profile from their trials coupled with favorable results from toxicology studies for their longer-term use support their evaluation with delamanid and bedaquiline in this trial.

The potential overlapping toxicities for the DBOS regimen requiring close monitoring include:

- Cardiac effects with QTc prolongation (delamanid, bedaquiline)
- Hepatic effects with increases in transaminases (bedaquiline, sutezolid)
- Nervous system effects, myelosuppression and lactic acidosis (potential class effects of oxazolidinones outlined in Section 3.2.2.2.1)

Section 3.2.3 outlines details on potential DDI for the individual drugs comprising the DBOS regimen. Important DDI to consider include concomitant medications inducing or inhibiting CYP3A4 which could affect delamanid and bedaquiline; such agents will be avoided for the trial. Additionally, inhibition of the monoamine oxidase inhibitors (MAO-A and MAO-B) is possible at the efficacious concentrations of sutezolid and its metabolite, PNU-101603, and medications from this class use will be avoided. Sparse PK samples of all drugs (and relevant metabolites) in

the experimental regimens will be obtained from patients during the trial and exposure to the various drugs will be monitored.

The staged design of the trial, the planned close monitoring throughout the assigned periods of treatment coupled with close follow-up and monitoring for relapse of TB post treatment, and the use of sites with a proven track record of conducting TB treatment trial with a high level of patient retention will support protection of patient safety and help determine the ultimate benefit:risk profile of these combinations.

3.3.2. Pretomanid, Bedaquiline, OPC-167832 and Sutezolid (PBOS)

3.3.2.1. Supportive Evidence From Combination Evaluation: Pretomanid and Bedaquiline Without Oxazolidinone Agent

3.3.2.1.1. Efficacy

In DS-TB, a randomized control trial evaluating the effects of pretomanid and bedaquiline (administered with pyrazinamide) on treatment over 8 weeks relative to 2HRZE/4HR demonstrated the potential for treatment shortening of the combination (Tweed et al, 2019). In this trial, among the 180 patients randomized, the daily change in time to positive (TTP) growth of Mtb in the automated MGIT liquid culture system, was increased in the trial arm administered 1) pretomanid and bedaquiline with a loading dose of 400 mg QD for 2 weeks, then 200 mg thrice weekly for the remaining weeks of treatment at 4.87% and 2) pretomanid and bedaquiline as 200 mg daily throughout the treatment period at 5.17% relative to observed in the 2HRZE/4HR arm at 4.04%. The increase in bactericidal activity in the two pretomanid and bedaquiline combination arms (given in combination with pyrazinamide) was significantly different compared to 2HRZE/4HR.

3.3.2.1.2. Safety

Regarding safety findings from this trial evaluating pretomanid and bedaquiline (administered with pyrazinamide which could have contributed to the findings), a higher proportion of patients in the 2 pretomanid and bedaquiline arms discontinued trial medication (10% and 8%, respectively) as compared to the 2HRZE/4HR arm (3%). Hepatic enzyme elevations were the most common Grade 3 or 4 AEs and resulted in withdrawal of 10 patients – 8% in the pretomanid and bedaquiline loading dose arm and 5% in the pretomanid and bedaquiline 200 mg daily arm versus 2% in the 2HRZE/4HR arm. Serious treatment-related AEs occurred in 3% of patients in the pretomanid and bedaquiline loading dose arm and 2% in the 2HRZE/4HR arm. Although 4% of patients died, no deaths were considered related to treatment (Tweed et al, 2019).

3.3.2.2. Supportive Evidence From Combination: Pretomanid, Bedaquiline and Oxazolidinone (Linezolid)

3.3.2.2.1. Efficacy

As highlighted in Section 3.1.3, pretomanid was first approved in 2019 for use in combination with bedaquiline and linezolid for the treatment of adults with pulmonary XDR-TB and those with MDR-TB with limited treatment options. The approval was based on the clinical efficacy and safety data from the pivotal trial which evaluated 6 months of treatment and an extended post-treatment follow up period (Conradie et al, 2020). This open-label single arm trial included

109 participants with XDR-TB and TI/NR MDR-TB refractory to treatment with results compared to historical controls to demonstrate efficacy of the regimen. In the intent-to-treat analysis, at 6 months after the end of treatment, 98 patients (90%; 95% confidence interval, 83% to 95%) had a favorable treatment outcome and 11 patients (10%) had an unfavorable outcome, including 7 (6.4%) deaths and 2 (1.8%) relapses. Substantially lower treatment success for XDR-TB patients in South Africa (≤50%) was reported prior to the conduct of the trial (Olayanju et al, 2018). Results from the follow-on ZeNix trial that investigated 4 different linezolid dosing strategies (1200 mg daily for 6 months, 1200 mg daily for 2 months, 600 mg daily for 6 months, and 600 mg daily for 2 months) within the BPaL regimen demonstrated similar overall efficacy results with 89% of participants (range among the four arms of 84% to 93%) having a favorable outcome at 6 months after 6 months of BPaL (Conradie et al, 2022). This level of treatment success among XDR-TB, pre-XDR-TB, and TI/NR MDR-TB patients was achieved with a much shorter course of treatment than usually required for XDR-TB. Of note, while 85% of patients in Nix-TB required dose reductions or interruptions of the 1200 mg daily linezolid dose, much lower rates were observed in the ZeNix trial, ranging from 13% to 28% in the shorter and lower dose regimens. These results further support the possibility that pretomanid, bedaquiline and an oxazolidinone serving as a backbone for new regimen construction could lead to meaningful treatment shortening and allow for "pan-TB" treatment. Optimization of a safer oxazolidinone that can be consistently administered is an important component of future work building on the BPaL regimen.

3.3.2.2.2. Safety

Regarding safety findings for the pretomanid, bedaquiline and linezolid combination regimen in the pivotal trial, among the 109 patients enrolled, 88 (81%) experienced peripheral neuropathy (81%) and 52 (48%) experienced myelosuppression. Among these, a substantial number of patients required dose reductions and interruptions in the administration of linezolid, which typically occurred after 3 months and 2 months of treatment, respectively. Transaminase increases to >3 x ULN were reported in 16% of patients, 2 of whom met Hy's Law lab criteria, but both successfully resumed the treatment regimen. Six (5.5%) patients died during treatment and one additional death occurred during the follow-up period. Nineteen (17%) patients experienced a serious adverse event. All surviving patients completed the trial, although 7% required treatment interruptions due to elevated LFTs and 25% permanently discontinued linezolid due to neuropathy or myelosuppression. Only 16 (15%) patients completed 6 months of linezolid dosed at 1200 mg/day without a dose reduction or interruption. The dose of linezolid was only reduced if toxicities occurred. The regimen was also associated with optic neuropathy (2 patients), lactic acidosis, and QT prolongation (maximum QTcF increase of 10 msec at Week 16 but no patients had a QTcF >480 msec) (Conradie et al, 2020).

The follow-up ZeNix trial studied 4 different linezolid dosing strategies (1200 mg daily for 6 months, 1200 mg daily for 2 months, 600 mg daily for 6 months, and 600 mg daily for 2 months) within the BPaL regimen to assess if lowering the dose or duration of linezolid could maintain efficacy and reduce linezolid-associated adverse events. Rates of peripheral neuropathy decreased with lower linezolid doses and shorter duration (38% for 1200 mg for 6 months, 24% for 1200 mg for 2 months, 24% for 600 mg for 6 months, and 13% for 600 mg for 2 months). A similar effect was seen for worsening anemia (22% for 1200 mg linezolid for 6 months, 17% for 1200 mg for 2 months, 2% for 600 mg for 6 months, and 7% for 600 mg for 2 months) (Conradie et al, 2022).

The most common AEs occurring in >10% patients on this combination included peripheral neuropathy, acne, anemia, nausea, vomiting, headache, increased transaminases, dyspepsia, decreased appetite, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyltransferase, upper respiratory tract infection, hyperamylasemia, hemoptysis, back pain, cough, visual impairment, hypoglycemia, abnormal loss of weight, and diarrhea (National Institute of Diabetes and Digestive and Kidney Diseases, https://www.ncbi.nlm.nih.gov/books/NBK551729/ accessed 20 May 2021).

3.3.2.3. Dose Selection and Rationale for PBOS Combination Agents

Table outlines the dose and schedule for the combination agents included in PBOS to be used in the Phase 2b/c trial. The justification and rationale for the doses and schedule selected for each of the agents (pretomanid, bedaquiline, OPC-167832, and sutezolid) are provided herein.

Table 11 PBOS Regimen Components Dosing and Schedule

Regimen components	P	B	O	S
Dose and Schedule	200 mg QD for treatment duration	400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment weeks	30 mg QD for treatment duration	1200 mg QD for treatment duration

3.3.2.3.1. Pretomanid Dose Selection and Rationale

Based on the amalgam of clinical trial experience with treatment of both DS-TB and MDR-TB patients, pretomanid will be administered as per the Product Label - 200 mg QD for treatment duration (Pretomanid Product Label, 2019). Pretomanid is recommended to be taken with food per its Product Label.

3.3.2.3.2. Bedaquiline Dose Selection and Rationale

Based on the amalgam of clinical trial and real-world experience with treatment of both DS-TB and MDR-TB patients, bedaquiline will be administered as per the Product Label - 400 mg QD for 2 weeks, then 200 mg thrice weekly for the remaining weeks of treatment (Sirturo® Product Label, 2023). Bedaquiline is recommended to be administered with food per its Product Label.

3.3.2.3.3. OPC-167832 Dose Selection and Rationale

OPC-167832 will be administered at the same dose as for the DBOS regimen - 30 mg daily for the assigned duration of treatment. See Section 3.3.1.3.3 for the rationale supporting the selection of this dose. OPC-167832 should be administered with food (see Section 3.3.1.3.3 for rationale).

3.3.2.3.4. Sutezolid Dose Selection and Rationale

Sutezolid will be administered at the same dose as for the DBOS regimen - 1200 mg daily for the assigned duration of treatment. See Section 3.3.1.3.4 for the rationale supporting the selection of this dose. Sutezolid should be administered with food (see Section 3.3.1.3.4 for rationale).

3.3.2.4. Summary for PBOS

The totality of the compelling clinical data demonstrating substantial improvement in SCC associated with use of pretomanid and bedaquiline in DS-TB patients and with pretomanid,

bedaquiline and linezolid as an oxazolidinone agent resulting in treatment success of 90% in a patient population with severe disease and a high degree of drug resistance (XDR-TB) supports moving forward with evaluation of PBOS for treatment shortening potential for "pan-TB" treatment in this trial. Likewise, the results from the 14-day EBA trial for OPC-167832 highlighted in Section 3.2.1.2 and for sutezolid in Section 3.2.2.2 have demonstrated substantive bactericidal activity of these agents in DS-TB patients and supports the potential for additive effect in combination with pretomanid and bedaquiline. Although there is limited data on OPC-167832 and sutezolid when administered for longer than 2 weeks and/or in combination with other anti-TB agents, the favorable safety profile from their trials coupled with favorable results from toxicology studies for their longer-term use support their evaluation with pretomanid and bedaquiline in this trial.

The PBOS regimen replaces linezolid with sutezolid (with a potentially improved safety profile based on toxicology study findings) and adds a fourth drug, namely OPC-167832 as a fourth drug from a novel class of anti-tuberculosis agents. Clinically apparent liver injury has been reported with pretomanid-based therapies, but largely in regimens that included moxifloxacin or pyrazinamide or both (Tweed et al, 2021). Although the AE profile of the PBOS regimen is anticipated to be potentially more favorable than the safety profile of the approved pretomanid, bedaquiline, and linezolid regimen, the limited clinical experience with sutezolid and with OPC-167832 and the lack of experience with the combination regimen underscores the need for close monitoring especially for prolongations in the QTc interval, hepatic toxicity, neurotoxicity, and myelosuppression, and lactic acidosis, in addition to more readily monitorable AEs such as nausea and vomiting.

The potential overlapping toxicities for the PBOS regimen requiring close monitoring include:

- Cardiac effects with QTc prolongation (bedaquiline)
- Hepatic effects with increases in transaminases (pretomanid, bedaquiline, sutezolid)
- Nervous system effects, myelosuppression and lactic acidosis (potential class effects of oxazolidinones)

Section 3.2.3 outlines details on potential DDI for the individual drugs comprising the PBOS regimen. Important DDI to consider include concomitant medications strongly inducing or inhibiting CYP3A4 which could affect pretomanid and bedaquiline; such agents will be avoided for the trial. Additionally, inhibition of the monoamine oxidase inhibitors (MAO-A and MAO-B) is possible at the efficacious concentrations of sutezolid and its metabolite, PNU-101603, and medications from this class use will be avoided. Sparse PK samples of all drugs (and relevant metabolites) in the experimental regimens will be obtained from patients during the trial and exposure to the various drugs will be monitored.

Pretomanid caused testicular toxicity in rodents. In monkeys, there were no histopathologic findings attributable to pretomanid in 3 studies of 3, 3, and 9-months duration. In four pretomanid-containing clinical trials, including one of 26 weeks' duration, there were no changes in sex hormones among male participants that were attributed to pretomanid. Results from a recently completed trial focused on addressing the reproductive safety of pretomanid administered as part of the 6-month BPaMZ regimen to male DR-TB patients demonstrated no adverse effects

of the pretomanid-containing regimen on human spermatogenesis as measured by change in mean total sperm count and sperm concentration over 6 months (see Section 3.1.3.2.2.1).

The staged design of the trial, the planned close monitoring throughout the assigned periods of treatment coupled with close follow-up and monitoring for relapse of TB post treatment, and the use of high-performance sites with a proven track record of conducting TB treatment trial with a high level of patient retention will support protection of patient safety and help determine the ultimate benefit:risk profile of these combinations.

3.4. Overall Conclusions

The selection of the four-drug combination experimental regimens to be evaluated in this trial (DBOS and PBOS) adheres to the principle of the multidrug approach for treating Mtb as a complex pathogen first applied in the discovery of the current SOC (2HRZE/4HR) more than 40 years ago (Fox et al, 1999). These novel combinations of newer and potentially more potent anti-TB agents are anticipated to decrease treatment duration to a period substantially shorter than the 6 months required for 2HRZE/4HR as SOC (WHO, 2017a), as well as the treatment duration usually required for MDR-TB (often ≥9 months) (WHO, 2022).

The agents comprising DBOS and PBOS have complementary mechanisms of action with each agent serving an important bactericidal purpose. Delamanid and pretomanid are both from the nitroimidazole class and serve to disrupt MTB mycolic acid synthesis. Bedaquiline from the novel diarylquinoline class inhibits ATP generation in MTB by interfering with the F-ATP synthase activity. OPC-167832 inhibits DprE1, an essential enzyme for MTB cell wall biosynthesis, differentiating its mechanism of action from other available TB drugs. Sutezolid is a novel oxazolidinone antibiotic that inhibits growth of MTB by binding to the bacterial 50s ribosome and blocking microbial translation and protein synthesis.

As reviewed in Section 3.3.1 for DBOS and Section 3.3.2 for PBOS, though these combinations are novel and have not previously been evaluated in the clinic, the available supportive evidence does suggest that these regimens have potential for meaningful treatment shortening. Both regimens demonstrated improved bactericidal activity and reduced time to durable cure compared with HRZE in the relapsing mouse TB model. In addition, DBOS evaluated in the HFS-TB model demonstrated added benefit with a progressively faster time to extinction compared to the combinations of delamanid plus bedaquiline plus OPC-167832 and delamanid plus OPC-167832, and time to extinction for this 4-drug combination was nearly one-half of the duration for the standard regimen serving as the in-study control (see Section 2.1.1). Additionally, data from the randomized controlled DELIBERATE trial (Dooley et al, 2021) and a large real world cohort study of MDR-TB patients (Franke et al, 2021) support the added benefit of the combined use of delamanid and bedaquiline and the acceptability of combining the agents for treatment from a safety perspective. Similarly, for PBOS, the substantially improved treatment outcomes and shorter treatment time for XDR-TB (and MDR-TB with limited treatment options) demonstrated with the BPaL regimen (including linezolid as a potent oxazolidinone) are encouraging. With the substitution of sutezolid for linezolid with potentially the same or better treatment effect (and with a potentially cleaner safety profile) coupled with the addition of the very promising OPC-167832 agent (with a clean safety profile so far) could equate to even greater potency for treatment shortening and less toxicity for a “pan-TB” treatment.

These combinations of agents comprising DBOS and PBOS with their complementary mechanisms of action should also provide a higher barrier to the emergence of resistance to any of the individual agents among patients under treatment. In addition, the prevalence of resistance to each of the agents in the broader population of TB patients from which participants for this trial will be recruited is anticipated to be low. The 3 approved drugs – bedaquiline, delamanid, and pretomanid – first approved in 2012, 2014, and 2019, respectively, have only been registered for treatment of MDR-TB (and XDR-TB patients as a subset of MDR-TB patients) with relatively limited uptake for broader treatment of drug resistant patients until recently. Only in 2018 did WHO recommend bedaquiline and linezolid for wider use in the treatment of MDR-TB patients (WHO, 2020); delamanid and pretomanid are still recommended only for use in MDR-TB patients with limited treatment options (WHO, 2020). Based on the anticipated limited prevalence of resistance to the agents in DBOS and PBOS, if either regimen is successful in this trial, it could support "pan-TB" treatment.

The expected potential toxicities of the investigational regimens are well-defined and generally expected to be mild and readily managed with the careful monitoring plan (as outlined in Section 1.7, Table 3, Table 4) proposed to address them. The staged design of the trial, the planned close monitoring throughout the assigned periods of treatment coupled with close follow-up and monitoring for relapse of TB post treatment through 12 months post randomization, as well as the use of high-performance sites with a proven track record of conducting TB treatment trial with a high level of adherence support and patient retention will support protection of patient safety. Additionally, the duration-response design element to be executed in Stage 2 will help identify the shortest viable duration of either experimental regimen to carry forward for confirmation in Phase 3 that is comparable to a full course of treatment with the current SOC (2HRZE/4HR) assuming a thorough balance of overall benefit and risk of the experimental regimen support so doing.

4. OBJECTIVES AND ENDPOINTS

Objectives and endpoints are outlined in Section 1.4 and Section 11.3.

5. TRIAL DESIGN

5.1. Overall Trial Design

This is an interventional, multicenter, two-stage, Phase 2b/c, open-label, randomized trial to evaluate the following:

- Stage 1: the treatment shortening potential based on the safety and efficacy of the combination regimens of DBOS and PBOS, administered for 4 months, in participants with pulmonary DS-TB in comparison with the standard 2HRZE/4HR regimen as assessed by the unfavorable outcome status through end of treatment and through 12 months of post-randomization follow-up, as well as sustained sputum culture conversion to negative assessed during the treatment period and the 12 months of post-randomization follow-up
- Stage 2: the efficacy and safety of varying durations of administration (in the range of 2 to 4 months) of the combination regimen of DBOS or PBOS in comparison with the standard 2HRZE/4HR regimen as well as sustained sputum culture conversion to negative assessed at the end of 12 months post-randomization
- Stage 2: the safety profile of the combination regimen of DBOS or PBOS in participants with pulmonary RR/MDR-TB compared with that of the standard 2HRZE/4HR regimen for participants with DS-TB

In Stage 1, eligible participants with DS-TB will be randomized in a 1:1:1 ratio to 3 arms:

- Arm 1: delamanid + bedaquiline + OPC-167832 + sutezolid (DBOS) for 4 months (17 weeks)
- Arm 2: pretomanid + bedaquiline + OPC-167832 + sutezolid (PBOS) for 4 months (17 weeks)
- Arm 3: 2HRZE/4HR regimen for 6 months (26 weeks) (8 weeks of HRZE then 18 weeks of HR)

For Stage 1, the treatment shortening potential of the experimental regimens relative to 2HRZE/4HR will be based on unfavorable treatment outcome status. The assessment of treatment shortening potential of the experimental regimens will be based on clinical, radiographic, and microbiological response during and at the end of the 4-month (17 weeks) treatment period compared with 6 months (26 weeks) of 2HRZE/4HR. In addition to evaluating the status at end of treatment, unfavorable status based on truncated data at earlier milestone time points will be summarized to create snapshots of unfavorable outcome rates across time for each treatment group. Microbiological response will be assessed by sustained conversion of sputum culture from growth of Mtb to no growth as defined by 2 successive negative cultures at least 1 week apart. Time to culture conversion will also be assessed.

When the last Stage 1 participant has reached the end of treatment, each of the DBOS and PBOS regimens will be assessed for treatment shortening potential in DS-TB participants, which will be characterized by the proportion of participants with unfavorable status at Week 17 for DBOS and PBOS and Week 26 for 2HRZE/4HR as SOC as well as truncated unfavorable outcome rates at milestone timepoints for each treatment group (see Section 1.8.4 and Section 11.3.1). Because unfavorable status has a composite definition, summaries will also show which individual components of the composite outcome were met. The Stage 1 efficacy and safety results will be reviewed comprehensively to assess treatment shortening potential and benefit/risk. If neither

DBOS nor PBOS shows evidence of treatment shortening potential with an acceptable safety profile, the trial will stop and neither regimen will advance to Stage 2. If only one of the DBOS or PBOS regimens shows evidence of treatment shortening potential with an acceptable safety profile, that regimen will be considered for proceeding to Stage 2. If both DBOS and PBOS show evidence of treatment shortening potential with acceptable safety profiles, the regimen that is considered for proceeding to Stage 2 will be the one with the more favorable profile overall, including, but not limited to, an assessment of secondary efficacy endpoints, which incorporate data on post-treatment relapses, safety, tolerability, and alignment with the target regimen profile for a new, affordable, shorter, safer, and simpler TB treatment regimen to treat all TB patients regardless of drug resistance status.

In Stage 2, eligible participants with DS-TB will be randomized in a 2:2:2:2:1:1 ratio to 6 arms:

- Arm 1: XBOS for 2 months (9 weeks)
- Arm 2: XBOS for 2.5 months (11 weeks)
- Arm 3: XBOS for 3 months (13 weeks)
- Arm 4: XBOS for 3.5 months (15 weeks)
- Arm 5: XBOS for 4 months (17 weeks)
- Arm 6: 2HRZE/4HR regimen for 6 months (26 weeks)

For this stage, the assessment will focus on unfavorable outcome measured 12 months post-randomization (ie, treatment failure, post-treatment relapse of disease, or death; traditional endpoints for Phase 3 TB treatment trial). A regression model will be used to characterize the relation between regimen duration and unfavorable outcomes assessed at 12 months post-randomization. The regression model will be used to estimate the appropriate duration of the XBOS regimen needed to observe non-inferiority in unfavorable outcomes compared to 2HRZE/4HR in a Phase 3 setting. An additional approximately 35 eligible participants with RR/MDR-TB (but not fluoroquinolone resistance) will be enrolled into a cohort given 4 months (17 weeks) of the XBOS regimen in Stage 2 in order to compare with the safety profile of the 2HRZE/4HR regimen in DS-TB participants.

Trial participation in all arms will consist of a screening period lasting up to 10 days and trial visits through 12 months post-randomization. Participants will be monitored with a robust set of clinical, laboratory, microbiologic, and radiologic elements focused on efficacy and safety during both the active treatment and post-treatment periods. A structured monitoring framework specifically designed to support participant safety will be utilized given that two of the regimen compounds are investigational and the investigational regimen durations are shorter than what is typically given for TB. Details on this monitoring framework and the supportive review process are provided in Section 9.5.4 and Section 1.6. Participants will be followed beyond 12 months post-randomization if their Month 12 sputum culture is positive for Mtb or if they have an active SAE or AESI at their Month 12 study visit.

The trial will be conducted at multiple sites in up to 6 countries. Stage 1 will be conducted in approximately 10 to 13 sites, in approximately 3 countries with diverse geographic representation likely in Africa, Asia, and South America. Stage 2 will be conducted in approximately 16 sites in about 6 countries in total.

See Section 1.3 for more detailed description of the trial design and Section 1.3.1 for a schematic of the trial design. Trial procedures are summarized in the Schedule of Activities (SoA) flowcharts Table 3 and Table 4 in Section 1.7 and detailed descriptions are in Section 9.

5.2. Justification for Dose

See Section 3.3.1.3 and Section 3.3.2.3 for justification of DBOS and PBOS dosing, respectively. WHO treatment guidelines from 2010 (which remain current) and current national TB treatment guidelines in the countries where trial sites are located serve as the basis for dosing of each anti-TB drug comprising the SOC regimen (2HRZE/4HR) as featured in Section 1.3.6, Table 1b (WHO, 2010; WHO, 2017a; Peru Ministry of Health, 2013; Philippines Department of Health, 2020; Republic of South Africa Department of Health, 2014).

5.3. End of Trial Definition-

A participant is considered to have completed the trial if they complete the final scheduled visit at Month 12 post randomization. The end of the trial is defined as the date of the last visit of the last participant in the trial or last scheduled procedure shown in the SoA (Section 1.7) for the last participant in the trial.

6. TRIAL POPULATION

This will be a multi-site international trial enrolling participants 18 to 65 years of age (inclusive) of both sexes with suspected pulmonary TB in the catchment area served by the trial sites. In Stage 1, only participants with DS-TB will be enrolled. In Stage 2, participants with DS-TB as well as those with RR/MDR-TB (but without fluroquinolone resistance) will be enrolled. Pregnant or breast-feeding women will be excluded from the trial because of uncertainties about the safety of pretomanid, OPC-167832, and sutezolid in these groups.

Stage 1 will enroll participants at approximately 10 to 13 trial sites in approximately three geographically diverse regions (currently planned to include sites in the Philippines, South Africa, and Peru). Additional trial sites and countries may be added for Stage 2. Participants will be recruited from communities with known high burdens of TB transmission and disease. Various methods of recruitment may be used, such as community information sessions, advertising, referrals, word-of mouth, or solicitation through participants previously known to the clinical site. The recruitment strategy is expected to result in trial participants who are representative of the local communities at trial sites in terms of demographic, socioeconomic, and clinical characteristics. Recruitment materials, if any, will be approved by the appropriate Institutional Review Board/s (IRBs) or Independent Ethics Committee/s (IECs). Interested participants will be invited to participate in the informed consent process.

6.1. Inclusion Criteria

For Stage 1, participants are required to meet all of the following inclusion criteria when assessed:

1) Able to provide written, informed consent prior to initiation of any trial-related procedures or treatments, and able, in the opinion of the Investigator, to comply with all the requirements of the trial.
2) Male or female participants between 18 and 65 years of age (inclusive) at the screening visit.
3) Body weight ≥35.0 kg and body mass index (BMI) ≥16.0 at the screening visit.
4) Newly diagnosed within the past 8 weeks prior to informed consent, untreated (≤4 days of treatment), drug-susceptible pulmonary TB, as defined by all of the following:
   a) Confirmation of Mtb infection: Mtb positivity on a molecular test (eg, Xpert Ultra, Hain LPA) conducted on a sputum specimen for trial screening
   b) Evidence of non-paucibacillary disease: ≥1+ sputum smear positivity for acid-fast bacilli using fluorescent microscopy, as defined by the International Union Against Tuberculosis and Lung Disease (IUATLD)/WHO scale, OR a Xpert Ultra semi-quantitative result of ‘medium’ or ‘high’ on the sputum specimen for trial screening
   c) Drug-susceptible TB: Isoniazid and rifampicin resistance not detected, as determined by a molecular test (eg, Hain LPA, Xpert Ultra, Xpert MTB/XDR) conducted on a sputum specimen for trial screening
   d) Clinical signs and/or symptoms consistent with active TB in the opinion of the Investigator
   e) Chest radiograph consistent with active TB in the opinion of the Investigator. Note, the Investigator is permitted, but not required, to incorporate a radiologist’s interpretation into their assessment of a participant’s chest radiograph

5) Able to spontaneously produce sputum.
6) Female participants of childbearing potential (FOCBP) must agree to use 2 approved methods of contraception with their male sexual partners or abstain from heterosexual intercourse throughout their participation in the trial (see Section 13.3).
7) Male participants must agree to use an approved method of contraception with their female sexual partners of childbearing potential or abstain from heterosexual intercourse throughout their participation in the trial (see Section 13.3).

For Stage 2, inclusion criteria #4 will be changed to the following:

4) Newly diagnosed within the past 8 weeks of informed consent, untreated (≤4 days of treatment), drug-susceptible or rifampicin-/multi-drug resistant pulmonary TB, as defined by all of the following:
   a) Confirmation of Mtb infection: Mtb positivity on a molecular test (eg, Xpert Ultra, Hain LPA) conducted on a screening sputum specimen
   b) Evidence of non-paucibacillary disease: ≥1+ sputum smear positivity for acid-fast bacilli using fluorescent microscopy, as defined on the IUATLD/WHO scale, OR Xpert Ultra semi-quantitative result of 'medium' or 'high' on the sputum specimen for trial screening
   c) Resistance pattern:
      i. For DS TB arm, isoniazid and rifampicin resistance not detected on a molecular test (eg, Hain LPA, Xpert Ultra, Xpert MTB/XDR) conducted on a screening sputum specimen, OR
      ii. For RR/MDR TB arm, either rifampicin resistance (RR TB) OR rifampicin and isoniazid resistance (MDR TB) detected on a molecular test (eg, Hain LPA, Xpert Ultra, Xpert MTB/XDR) conducted on a screening sputum specimen
         - Participants with RR or MDR TB must also have fluoroquinolone resistance not detected, as determined by a molecular test (eg, Hain LPA second line, Xpert MTB/XDR) performed on the sputum specimen for trial screening
   d) Clinical signs and/or symptoms consistent with active TB in the opinion of the Investigator
   e) Chest radiograph consistent with active TB in the opinion of the Investigator

The other inclusion criteria remain the same for Stage 2.

6.2. Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply.

1) Suspected or documented extra-thoracic TB. Confirmed or suspected lymph node TB is not considered exclusionary. The presence of a pleural effusion considered not clinically significant together with pulmonary TB is not exclusionary.
2) Known, or suspected of having, resistance to a rifamycin, isoniazid, ethambutol, pyrazinamide, delamanid, pretomanid, bedaquiline, linezolid, tedizolid, or sutezolid either confirmed by the laboratory, or based on epidemiological history, such as a known source case with said resistance.

3) Received any prior treatment for active Mtb disease (>4 days) within the past 1 year of informed consent.
4) Received any treatment with a fluoroquinolone active against Mtb (ie, levofloxacin, moxifloxacin, ciprofloxacin) or an aminoglycoside for more than 14 days within the 3 months prior to informed consent even if the medication was given for a different indication than TB treatment.
5) Any known prior exposure to delamanid, pretomanid, bedaquiline, OPC-167832, or any oxazolidinone (linezolid, tedizolid, delpazolid, or sutezolid).
6) Evidence of an active clinically significant/uncontrolled metabolic, gastrointestinal, neurological (including peripheral neuropathy), psychiatric, endocrine (including uncontrolled diabetes), hematologic, ophthalmologic (particularly optic neuritis), or liver disease; active malignancy; or other medical co-morbidity considered significant enough by the Investigator that the participant should not enter the trial.
7) Significant history of, or current clinically relevant cardiovascular disorder, such as heart failure, coronary artery disease, uncontrolled hypertension, arrhythmia, tachyarrhythmia, prolonged QT syndrome, or presence of symptom(s) strongly suggestive of such a problem, such as exertional chest pressure/pain or unexplained syncope.
8) Significant history of, or current evidence of an active clinically significant/poorly controlled pulmonary disease, such as asthma, COPD, silicosis, or lung fibrosis (other than TB), considered as severe by the Investigator. In particular, any underlying pulmonary condition that could significantly interfere with the assessment of X-ray images, interpretation of sputum findings, or otherwise compromise the participant's participation in the trial is exclusionary based on the Investigator's judgement. Clinically significant post-COVID-19 pulmonary sequelae should be considered exclusionary.
9) If HIV-infected, having any of the following present:
    a) Not on antiretroviral treatment at time of screening or taking antiretroviral treatment for <3 months prior to screening, OR
    b) CD4+ T-cell count <200 cells/µL during the screening period, OR
    c) HIV viral load >200 copies/mL during the screening period, OR
    d) Evidence of a currently active opportunistic malignancy or infection related to HIV other than TB that requires treatment with a prohibited concomitant medication (oral candidiasis is not exclusionary), OR
    e) HIV-infected participants enrolling at a trial site in Peru will not be eligible due to the requirement for longer TB treatment courses than the standard 6-month HRZE regimen for patients with HIV/TB co-infection as per the Peruvian national TB treatment guidelines.
10) If female, currently pregnant or breastfeeding, OR having a positive serum or urine pregnancy test during the screening period, OR planning to become pregnant within the 12-month period after the screening period. Refer to Section 13.3 (Appendix 3, Section 13.3) for more information.
11) Current significant drug and/or alcohol abuse that is likely to result in poor adherence to trial requirements or that would pose a risk to the participant's wellbeing during the trial.
12) Karnofsky Performance Status scale score at screening of <60.
13) Having a disease or condition where the use of delamanid, pretomanid, bedaquiline, OPC-167832, sutezolid, rifampicin, isoniazid, pyrazinamide, or ethambutol is contraindicated.

14) Positive SARS-CoV-2 PCR result on nasopharyngeal sample taken during screening. Prior history of COVID-19/SARS-CoV-2 infection is not exclusionary if SARS-CoV-2 PCR performed on screening sample is negative.
15) Any of the following laboratory results during screening:
    a) Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2
    b) Alanine transaminase (ALT) or aspartate transaminase (AST) >2.5 × upper limit of normal of the clinical laboratory reference range
    c) Total bilirubin >2x upper limit of normal of the clinical laboratory reference range, at screening
    d) Hemoglobin <8.0 gm/dL
    e) Platelet count <100 x 10^9/L
    f) White blood cell count <2.0 x 10^9/L
    g) Screening glycosylated hemoglobin (HbA1c) ≥10.0%
    h) Positive hepatitis B surface antigen
    i) Positive hepatitis C antibody
16) Moderate to severe substance use disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (substances of concern may include cocaine, amphetamines, opiates, barbiturates, benzodiazepines, or alcohol)

    Note: it is not exclusionary if a participant has been prescribed the drug for which they test positive by a medical practitioner. Also, screening will be conducted for cannabinoids, however, a positive test for cannabinoids is not exclusionary.
17) A clinically significant ECG abnormality at screening as confirmed by a central ECG reading service. Examples of such include, but are not limited to, second- or third-degree atrioventricular block, complete right bundle branch block, left bundle branch block, QRS duration ≥120 msec, QTcF interval >450 msec in males or >470 msec in females, atrial fibrillation or flutter, supraventricular tachycardia, and ventricular tachycardia or multiple multifocal premature ventricular complexes.

    The following ECG findings are not considered clinically significant: sinus tachycardia, mild first-degree atrioventricular block (P-R interval <0.23 sec), right or left axis deviation, incomplete right bundle branch block, and isolated left anterior fascicular block (left anterior hemiblock) in young otherwise healthy participants.
18) Participants receiving any of the prohibited medications (see Section 7.5.1) within the specified periods or who would be likely to require prohibited concomitant therapy during the trial.
19) History of having taken another investigational drug within 30 days preceding trial entry or participates in another clinical study during the duration of this trial.

Prospective approvals of protocol deviations to enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

Participants with baseline culture results (defined as collected during screening period through up to Week 1) that are all negative for growth of Mtb will not be included in efficacy analyses (see Section 11.1).

DS-TB participants whose baseline phenotypic DST results demonstrate resistance to isoniazid and/or rifampicin will not be included in efficacy analyses. Their treatment will be modified accordingly based on their resistance profile, relevant local/national guidelines, and the participant's interest to continue in the trial after discussion with the Investigator (see also Section 8.3.2).

6.3. Lifestyle Considerations

Female participants of childbearing potential will be required to agree to use two forms of accepted birth control with their male sexual partners during their participation in the trial or remain abstinent throughout their participation in the trial. Male participants will be required to agree to use an accepted form of birth control with their female sexual partners throughout their participation in the trial. See Section 6.1 and Section 13.3.

A participant's social circumstances should be assessed during screening to ensure, as much as possible, that the participant is planning to continue living within a trial site's catchment area throughout their 12-month trial participation.

6.4. Screening

Screening assessments can be done at any time during the screening window except for written informed consent, which must be completed prior to any screening procedure.

6.4.1. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to trial intervention/entered in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Study (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (ie, why eligibility criteria were not met), and any SAE.

6.4.2. Re-screening

Screening procedures may be repeated if there are technical or operational difficulties with collection, processing, or running of screening laboratory tests (e.g., laboratory reports hemolyzed blood or sputum container leaks) or conducting a screening procedure (e.g., ECG machine error) if the repeat screening procedure can be completed within the original screening window.

Investigators may review rescreening eligibility on a case-by-case basis with the Sponsor.

7. TRIAL INTERVENTIONS

Trial intervention is defined as any investigational intervention(s) or marketed product(s) intended to be administered to a trial participant according to the trial protocol.

7.1. Trial Interventions Administered

7.1.1. Investigational Agents Composition and Administration

In this trial, delamanid, bedaquiline, OPC-167832, and sutezolid (DBOS) and pretomanid, bedaquiline, OPC-167832, and sutezolid (PBOS) will be administered as investigational regimens. The composition of each investigational product is provided in Table 12 below. Participants will be instructed to take all trial medications within 1 hour of ingesting food.

The commercially marketed investigational products (delamanid, pretomanid, bedaquiline) will be packaged/repackaged in blisters or bottles as needed to support this clinical trial. The clinical stage investigational products (sutezolid and OPC-167832) will be packaged in blisters or bottles as supported by product quality data. The investigational products will be dispensed as a combination of blister-packaged and bottle packaged products to suit the dosing, visit schedules, and the adherence methods.

Table 12 Investigational Product Composition and Formulation

Active Ingredient	Formulation	Inactive Ingredients
Deltyba® (Delamanid)	Film-coated tablet containing 50 mg of delamanid	Tablet Core: Hypromellose phthalate, povidone, tocopherol, microcrystalline cellulose, sodium starch glycolate, carmellose calcium, light anhydrous silicic acid, magnesium stearate, lactose hydrate Film Coating: Hypromellose, macrogol 6000, titanium oxide, talc, yellow ferric oxide
Pretomanid	Tablet containing 200 mg of pretomanid	Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate
Sirturo (Bedaquiline)	Tablet containing 120.89 mg of bedaquiline fumarate drug substance equivalent to 100 mg of bedaquiline	Colloidal silicon dioxide, corn starch, croscarmellose sodium, hypromellose 2910 15 mPa.s, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, purified water (removed during processing)
OPC-167832	Immediate release tablet containing 3, 10, or 30 mg of OPC-167832	Lactose monohydrate, corn starch, colloidal silicon dioxide, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate
Sutezolid	Immediate release tablet containing 600 mg of sutezolid	Intra-granular: Maize starch B, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl cellulose, purified water (removed during processing) Extra-granular: Sodium starch glycolate and magnesium stearate

Active Ingredient	Formulation	Inactive Ingredients
The investigational products will be stored, shipped, and transported in conditions specified in their commercial labels and supported by data for clinical stage drugs (ie, sutezolid and OPC-167832) that will be specified both on the clinical label and in the Pharmacy Manual.		

7.1.2. Management of Investigational Product

The trial's investigational drugs will be dispensed in an unmasked (unblinded) fashion based on the randomization list by authorized and trained site staff members.

Participants will be randomized based on a randomly generated sequence of participant identification (identifier) numbers (randomization schedule) using a validated Interactive Voice/Web Response System (IVRS/IWRS). Before the trial is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and instructions for the IWRS will be provided to the trial sites.

7.1.3. Management of Standard of Care

The 2HRZE/4HR combination is approved, indicated, and commonly used as a 6-month treatment for DS-TB patients. Participants randomized to the 2HRZE/4HR control arm in this trial will be given standard weight-adjusted doses of HRZE. See the HRZE package insert for more information (Rimstar SmPC, 2021) and Table 1b.

7.2. Preparation/Handling/Storage/Accountability

7.2.1. Storage

The trial pharmacist (or designee) must confirm appropriate temperature conditions have been maintained during transit and during site storage for all study drugs received and that any discrepancies are reported and resolved before use. Upon receipt of study drug supplies, the trial pharmacist (or designee) must immediately inspect supplies for damage. Any damage or discrepancy from the packing list must be documented and promptly discussed with the Sponsor or CRO representative to determine the appropriate action.

7.2.2. Accountability

Only participants enrolled in the trial may receive study drug and only authorized site staff may supply or administer study drug. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Authorization for any unused study drug and supplies to be destroyed is the responsibility of the Sponsor or delegated authority. Unused supplies will be destroyed according to the facility's SOPs or per local regulations. Any disposal of study drug conducted at the clinical site must be documented in the trial file.

Further guidance and information for the handling, storage, dispensing, and accountability are provided in the trial specific manual(s).

7.3. Measures to Minimize Bias: Randomization and Masking

7.3.1. Randomization

In Stage 1, participants will be randomized in a ratio of 1:1:1 to one of the following treatment arms:

- Arm 1 (N=43): DBOS for 4 months (17 weeks)
- Arm 2 (N=43): PBOS for 4 months (17 weeks)
- Arm 3 (N=43): 2HRZE/4HR for 6 months (26 weeks)

In Stage 2, DS-TB eligible participants will be randomized in a ratio of 2:2:2:2:1:1 to one of the following treatment arms:

- Arm 1 (N=70): XBOS for 2 months (9 weeks)
- Arm 2 (N=70): XBOS for 2.5 months (11 weeks)
- Arm 3 (N=70): XBOS for 3 months (13 weeks)
- Arm 4 (N=70): XBOS for 3.5 months (15 weeks)
- Arm 5 (N=35): XBOS for 4 months (17 weeks)
- Arm 6 (N=35): 2HRZE/4HR regimen for 6 months (26 weeks)

In Stage 2, RR/MDR-TB eligible participants will be enrolled into a cohort:

- XBOS in RR/MDR-TB participants (N=35) for 4 months (17 weeks)

Participants will be randomized based on a randomly generated sequence of participant identification (identifier) numbers (randomization schedule) using a validated Interactive Voice/Web Response System (IVRS/IWRS).

7.3.2. Masking (Blinding)

This trial will be open label for trial participants, trial site personnel, IDMC members, and Sponsor and CRO personnel. Microbiology lab personnel will be blinded to all trial participants' treatment assignments. STrAW Concilium members will be blinded to the specific regimen assignment among those randomized to receive an investigational regimen. It is not feasible to blind Concilium members from whether a participant was assigned an investigational regimen or standard of care due to their different durations of treatment and intensive and continuation phases for 2HRZE/4HR (see Section 1.6).

7.3.3. Masking Break

Not applicable in this trial.

7.4. Trial Intervention Adherence

Dosing (Stages 1 and 2)

Directly observed therapy (DOT) will be required for adherence monitoring and support in all trial arms in both stages. Specific DOT models utilized, such as home visits by treatment support workers or clinic-based DOT, will be determined by prevailing national guidelines and resources available at each trial site. In addition, video observed therapy (VOT) and medication event reminder monitors, will be used to support adherence and DOT (WHO, 2017a; WHO, 2017b; WHO, 2020). VOT is permitted to substitute for in-person DOT for verification of medication adherence. Doses on weekends and on holidays up to three consecutive days may be self-administered. Details of these measures will be specified in the Trial Operations Manual. Adherence data will be collected at each trial visit during the treatment period.

Dosing will be performed on an ambulatory basis. Participants will be instructed to take the component medications of DBOS and PBOS within 1 hour of ingesting food. Participants randomized to 2HRZE/4HR will be instructed to take the medicines more than 1 hour after ingesting food. Dosing schedule and requirements for Stage 1 are presented in Table 1a and Table 1b. Dosing schedule for Stage 2 for the regimen chosen to move forward with be the same as Stage 1, but duration will vary according to assigned arm (see Section 7.3.1).

7.5. Prior and Concomitant Therapy or Medications

Any prescription or over-the-counter medication, including anti-inflammatory and anti-pyretic drugs, that a participant takes from 30 days prior to signing trial informed consent through the end of trial will be recorded along with reason for use (eg, management of an AE), dates of administration, and dosage information. Information on AEs caused by medications (IMP or concomitant) will also be captured. Participants assigned to 2HRZE/4HR should be prescribed pyridoxine (vitamin B_6) to reduce the risk of peripheral neuropathy from isoniazid as per the applicable local or national guidelines where they are enrolled. This preventative measure is recommended by WHO and most national TB programs. Pyridoxine does not have any drug-drug interactions of concern with any study drugs. Participants assigned to the DBOS and PBOS arms do not require co-administration of pyridoxine due to the different mechanism by which oxazolidinones are believed to induce peripheral neuropathy (see Section 3.2.2.2.1), but the Investigator is permitted to prescribe it based on their clinical judgement. Receipt of COVID-19 vaccination during trial participation will also be collected through concomitant medication review.

7.5.1. Prohibited Therapies and Medications

No combination TB treatment will be administered during the Screening Phase. Participants are permitted to have taken a maximum of four days of TB treatment prior to signing informed consent. No additional treatment for TB other than study drugs (DBOS, PBOS, or HRZE) will be administered during the Treatment and Follow-Up Phase unless a participant is determined to have experienced treatment failure, TB relapse, re-infection with TB, or is identified to have a drug-resistant form of TB at baseline requiring treatment change. Initiation of TB preventive therapy (TPT) after the completion of study treatment is not permitted until a participant has completed their last study visit as TPT is likely to affect relapse. See Section 9.5.4 for more details.

Appendix 1 lists the medications not permitted from Day 1 through one month after completion of trial treatment. Participants who are found to be taking one of the disallowed medications during

the screening period will be assessed by the Investigator to determine if they can be safely transitioned to an equivalent drug not on the prohibited medication list. Participants who develop a medical condition during their trial participation that requires the administration of a prohibited medication will be discontinued from the trial (see Section 8.3.2). In addition, participants identified to be taking herbal agents during screening will be eligible for the trial if they agree to discontinue use of the agent(s) for the duration of the trial.

No vaccine that can be reasonably delayed until after the trial, including the Follow-up Phase, should be administered. Time-sensitive vaccinations are permitted, including for COVID-19, seasonal influenza, and post-exposure prophylaxis for tetanus and rabies. Such vaccinations will be captured in the concomitant medication and therapy log. Investigators should consult the Sponsor prior to administration of a non-urgent vaccine they believe a participant should receive.

7.5.1.1.1. Prohibited HIV Antiretrovirals and Management of Antiretroviral Treatment Regimen Changes After Randomization

It is expected that most HIV-infected participants screened for the trial will be taking antiretroviral treatment (ART) regimens containing dolutegravir with a smaller proportion on efavirenz or a ritonavir-boosted protease inhibitor containing regimen. Dolutegravir is preferred over efavirenz and protease inhibitors given their drug interaction profiles.

Dolutegravir levels are reduced by rifampicin's strong CYP3A4 induction, but clinical trials have demonstrated preserved potency of dolutegravir-based ART in TB co-infected patients taking rifampicin when the dolutegravir dose is increased from 50 mg QD to 50 mg BID. Efavirenz is on the prohibited medication list because of its induction of CYP3A4 enzymes, which lowers bedaquiline levels. Protease inhibitors are disallowed because of their CYP3A4 inhibition, which can increase bedaquiline levels, and because rifampicin's strong CYP3A4 induction significantly lowers protease inhibitor levels. Additional ritonavir boosting is often attempted in DS-TB/HIV co-infected individuals on protease inhibitor-based regimens to counteract rifampicin's CYP3A4 induction with variable and unpredictable results. Additional antiretrovirals (ARVs) that have significant drug-drug interactions with one or more trial medications are nevirapine (CYP3A4 substrate), rilpivirine (CYP3A4 substrate), and etravirine (CYP3A4 inducer and substrate), but are not expected to be encountered frequently in the trial. Raltegravir may also be encountered in screened participants; raltegravir levels are also reduced by rifampicin and a dose increase from 400 mg BID to 800 mg BID is recommended.

Based on these interactions, efavirenz, nevirapine, all protease inhibitors, rilpivirine, and etravirine will not be permitted during the trial. HIV-infected participants taking efavirenz, a protease inhibitor, nevirapine, rilpivirine, or etravirine at screening who are otherwise eligible for the trial can be randomized if the prohibited ARV can be safely substituted with dolutegravir (or raltegravir) as judged by the Investigator. Table 10 specifies the required ARV adjustments after randomization.

Table 10 Management of Antiretroviral Substitutions for Drug-Drug Interactions

ARV at Screening	Assigned TB Regimen	ART Management[a]	Washout Period
Dolutegravir	DBOS or PBOS	No substitution required	N/A
	2HRZE/4HR	No substitution required but dolutegravir dose should be increased to 50 mg twice daily when rifampicin is started	N/A
Efavirenz	DBOS or PBOS	Substitution required with a preferred INSTI	Start TB regimen after 7-day EFV washout
	2HRZE/4HR	Substitution required with a preferred INSTI	No washout required
Protease inhibitor (any)	DBOS or PBOS	Substitution required with a preferred INSTI	Start TB regimen after 3-day PI washout
	2HRZE/4HR	Substitution required with a preferred INSTI	No washout required
Nevirapine	DBOS or PBOS	Substitution required with a preferred INSTI	No washout required
	2HRZE/4HR	Substitution required with a preferred INSTI	No washout required
Raltegravir	DBOS or PBOS	No substitution required	N/A
	2HRZE/4HR	No substitution required but raltegravir dose should be increased to 800 mg twice daily when rifampicin is started	N/A

a Choice of ARV with which to substitute should be based on a participant's complete ART history, including any available resistance test results.

INSTI=Integrase inhibitor. Preferred integrase inhibitors are dolutegravir followed by raltegravir.
EFV=efavirenz; PI=protease inhibitor.

7.6. Dose Modification

The dose of 2HRZE/4HR should be adjusted, as needed, for the participant's current weight recorded at the most recent trial visit per the dosing guidance in Section 1.3.6. No dose modifications of 2HRZE/4HR are allowed for management of AEs believed to be caused by one or more medications in the 2HRZE/4HR regimen. Gradual, stepwise re-introduction of 2HRZE/4HR regimen components is permitted after temporary interruption, such as after an AE (see Section 8.3.1).

The dose of sutezolid may be reduced to 600 mg QD for the management of myelosuppression and peripheral neuropathy when sutezolid has been judged to be at least a reasonably possible cause of the toxicity. An Investigator must first discuss the dose reduction with the medical monitor/Sponsor although temporary interruption of sutezolid upon identification of a Grade 3 or higher AE or SAE believed to be due to sutezolid is permitted to protect participant's safety. Participants who develop signs or symptoms of optic neuritis should have sutezolid or ethambutol immediately withheld depending on their assigned regimen pending further evaluation. Participants with confirmed optic neuritis should not be rechallenged with sutezolid or ethambutol.

7.7. Intervention After the End of the Trial

There is no intervention planned after the end of the trial.

8. INTERRUPTION AND DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1. Pausing and Termination of Individual Site and Entire Trial

The Sponsor can temporarily pause or permanently terminate the trial or one or more of the trial arms. The IDMC can also recommend a temporary pause or permanent termination of the entire trial or one or more of the trial arms to the Sponsor. The Sponsor, IDMC, site Investigators, or ethics committees can temporarily pause or permanently terminate trial participation at individual sites if determined to be necessary for medical, safety, regulatory, ethical, or other reasons. In the event of a trial pause or termination, the Sponsor will immediately notify all Investigators, IDMC, ethics committees, and regulatory authorities as required. If an Investigator initiates a trial pause or termination at their site, they must notify the Sponsor within 24 hours. A trial pause due to safety concerns will prompt an ad hoc IDMC meeting to review relevant safety data and make a recommendation to the Sponsor on how to proceed. The Sponsor will make the final decision whether to resume trial activities with or without protocol amendments.

8.2. Individual Participant Withdrawal From the Trial

Each participant has the right to withdraw consent to further participation in the trial at any point for any reason. A participant's withdrawal of consent applies to future participation in the trial and use of any participant data from the date of consent withdrawal and after. They may also request destruction of any samples taken and not tested. Withdrawal of consent conveys that the participant refuses to be followed up by any means proposed by the Investigator and Sponsor. The Investigator should ask the participant why they want to withdraw consent in order to identify possible modifications that would permit the participant to remain in the trial. The Investigator should obtain written confirmation of the participant's desire to withdraw consent and reasons for withdrawal, if possible. Where written confirmation is not obtained, trial staff should document any reasons provided by the participant. See Section 13.2 (Appendix 2) regarding the participants' right to withdraw.

Each participant also has the right to permanently stop trial treatment yet continue their participation in the trial (see Section 8.3.2).

An Investigator may also withdraw a participant from the trial at any time for medical, safety, behavioral, compliance, administrative, or other reasons. The participant will be permanently discontinued from the trial treatment and withdrawn from the trial at that time. The Investigator should clearly document the reasons for withdrawing a participant from the trial.

8.3. Individual Participant Treatment Interruption, Resumption, and Permanent Discontinuation

Temporary interruption or permanent discontinuation of trial treatment may occur for a variety of reasons, including, but not limited to an AE, treatment failure or disease relapse, required treatment with a disallowed concomitant medication or therapy, Investigator clinical discretion, pregnancy, withdrawal of consent, or being lost to follow-up. The treatment interruption or permanent discontinuation may be initiated by the participant, Investigator, or Sponsor.

8.3.1. Trial Treatment Interruption and Resumption

8.3.1.1. General Guidance on Treatment Interruption

Participants that temporarily interrupt their trial treatment due to non-medical reasons, such as a missed trial visit, should resume their full treatment regimen as soon as possible.

Investigators should make thorough assessments before interrupting one or more of a participant's trial medications implicated as a possible cause of an AE (See Section 10.2.1). If, after their careful assessment, an Investigator determines a toxicity is at least possibly attributable to study drug(s), the suspected drug(s) may be temporarily withheld. For higher severity toxicities (eg, Grade 3 or 4), Investigators should utilize a lower threshold when deciding whether to temporarily interrupt study drug(s). Study drug(s) should be restarted as soon as possible based on the Investigator's judgement when it is safe to resume. Sequential reintroduction of study drugs, including SOC, (and essential concomitant medications) should be considered when it is not clear which drug, if any, caused the toxicity. The schedule of drug reintroduction is at the discretion of the Investigator. See Section 10.2.1 for general guidance on the management of adverse events.

8.3.1.2. Specific Guidance on Treatment Interruption

8.3.1.2.1. Cardiotoxicity

Participants receiving DBOS or PBOS observed to have a QTcF interval >500 msec that is confirmed on at least two ECGs and by a central reader should have their full regimen temporarily withheld pending further investigations and management of any alternate causes of QT interval prolongation identified. Resumption of trial treatment should be based on the subsequent ECG results and the Investigator's judgement. The Investigator may consult the Sponsor for guidance.

8.3.1.2.2. Hepatotoxicity

Participants observed to have any of the following liver transaminase elevations should have their full TB regimen temporarily withheld pending further investigation and management of any alternate causes of liver injury identified:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for >2 weeks
- ALT or AST >3x ULN and total bilirubin >2x ULN or INR >1.5
- ALT or AST >3x ULN and clinical symptoms/signs of hepatitis (fatigue, anorexia, nausea, vomiting, right upper quadrant pain/tenderness, hepatomegaly, jaundice, and/or dark urine) or a systemic hypersensitivity reaction (fever, rash, and/or eosinophilia [>5%])

ALT/AST values >3x ULN and total bilirubin values >2x ULN should be repeated as soon as possible to confirm the degree of elevation before interrupting treatment except when ALT/AST values are significantly elevated to >8x ULN in which case immediate treatment interruption is recommended while awaiting confirmatory tests and additional investigations. Resumption of trial treatment should be based on subsequent liver enzyme results and the Investigator's judgement. The Investigator may consult the Sponsor for guidance. Participants meeting Hy's Law criteria should not be rechallenged with trial treatment without the Sponsor's approval. Hy's Law criteria (U.S. Food and Drug Administration. Guidance for Industry) are:

- ALT or AST >3x ULN (hepatocellular injury) and
- Total bilirubin >2x ULN (altered hepatic function) and
- Alkaline phosphatase (ALP) <2x ULN (no initial evidence of cholestasis) and
- No other reason for elevated ALT/AST and bilirubin identified, such as viral, autoimmune, or alcoholic hepatitis, non-alcoholic steatohepatitis, or another hepatotoxic drug

8.3.1.3. Impact of Treatment Interruptions on Assessment of Regimen Adherence

For purposes of assessing participants' adherence to their assigned regimen when one or more drugs in their regimen have been interrupted, the following considerations will be made. Additional details will be specified in the Statistical Analysis Plan for the trial:

- DBOS and PBOS regimens
  - Participants taking 0, 1, or 2 study drugs on a calendar day are counted as not taking their regimen on that day
  - Participants taking 3 or 4 study drugs on a calendar day are counted as taking their regimen on that day
  - Note: Since bedaquiline will be prescribed 3 times per week after the initial 14-day load, a participant will be considered to have taken bedaquiline on the other four days they are not scheduled to take it if bedaquiline is actively prescribed in their file.
- 2HRZE/4HR regimen
  - Intensive phase
    - Participants taking 0, 1, or 2 drugs on a calendar day are counted as not taking their regimen on that day
    - Participants taking 3 or 4 drugs on a calendar day are counted as taking their regimen on that day
  - Continuation phase
    - Participants taking 0 or 1 drug on a calendar day are counted as not taking their regimen on that day
    - Participants taking 2 drugs on a calendar day are counted as taking their regimen on that day.

8.3.2. Permanent Discontinuation of Trial Treatment

Randomized participants who meet one or more of the following criteria will be discontinued from trial treatment:

- Pregnancy
- Participant request for permanent discontinuation of trial treatment
- Any clinical adverse event, laboratory abnormality, intercurrent medical condition or illness, new requirement for a concomitant medication on the excluded medication list, or other situation where an Investigator determines that continued administration of trial treatment is not in the best interest of the participant
- Treatment failure based on Investigator judgement (with STrAW Concilium consultation, see Section 1.6)

- **For participants randomized to 2HRZE/4HR arm only:** Baseline sputum culture phenotypic drug susceptibility testing demonstrates resistance to rifampicin and/or isoniazid (Note: all DS-TB participants require screening results documenting no resistance identified to rifampicin and isoniazid on rapid molecular test(s) prior to randomization). These participants should be referred to their local DR-TB program for appropriate management. Participants randomized to DBOS or PBOS who are subsequently found to have rifampicin or isoniazid resistance may remain on their assigned regimen since presence of rifampicin or isoniazid resistance does not affect the anti-TB activity of agents in DBOS and PBOS. Participants found to be resistant to pyrazinamide or ethambutol are not required to change their treatment regardless of whether they are receiving 2HRZE/4HR, DBOS, or PBOS.

Investigators should discuss decisions regarding the permanent discontinuation of one or more trial investigational medications for a participant with the STrAW Concilium and inform the Sponsor (see Section 1.6). TB treatment should not be permanently changed, stopped, or restarted before consultations with the STrAW Concilium have been completed if the participant's clinical condition permits. See Section 9.5.4 for further details of the evaluation and management of participants permanently discontinued from trial treatment.

Investigators are not required to permanently discontinue a participant from trial treatment once a certain threshold of missed regimen days is reached per the regimen adherence definitions. They should use their clinical judgement to determine if the participant has experienced treatment failure (see fourth bullet point above). However, trial treatment cannot be extended more than 5 days beyond the randomized treatment duration to make up missed regimen days or doses regardless of the reason for missed doses. Participants with significant regimen non-adherence (for any reason) will be addressed in the Per Protocol analysis population (detailed in the trial Statistical Analysis Plan). As stated in Section 8.3, the decision to permanently discontinue trial treatment for an individual participant can be made by the participant, Investigator, or Sponsor.

After discontinuation of trial treatment, standard 2HRZE/4HR therapy for DS-TB will be initiated per local guidelines and further tailored as needed based on available drug susceptibility testing results from the most recent sputum cultures positive for Mtb growth, if any. For participants discontinuing trial treatment in the RR/MDR-TB cohort, an individualized regimen will be started based on local guidelines and available drug susceptibility testing results from the most recent sputum cultures positive for Mtb growth, if any.

Participants for whom trial treatment has been permanently discontinued will continue to be followed in the trial to permit collection of safety data unless they withdrawal consent for trial participation.

8.4. Lost to Follow-up

Site trial staff should make multiple efforts to contact participants that miss scheduled trial visits and adherence checks (eg, daily VOT videos or DOT visits). Participants missing a visit during trial treatment should be contacted by phone. If they cannot be reached by phone, a home visit should be promptly conducted (no later than 3 days) after the missed visit. If a participant misses

a scheduled trial visit during the post-treatment follow-up period and they cannot be reached by phone, a home visit should be conducted within 1 week. If a participant misses their final scheduled trial visit at Month 12, multiple attempts must be made to contact them, including home visits, to verify their vital status.

Before a participant is deemed lost to follow up, the site should make at least 3 attempts to regain contact with the participant by phone and, if necessary, home visits by a member of the trial team. These contact attempts should be documented in the participant's medical record. A participant should be considered lost to follow-up if all attempts to contact them or verify their status are unsuccessful by the time of the Month 12 visit of the last trial participant.

Vital status can be determined from a variety of sources. Acceptable documentation of death includes death certificates, medical records, public records, and statements by a family member or treating physician. Acceptable documentation of life includes, but is not limited to, direct contact with the participant, medical records, successful phone contact with the participant, public records, and statements by a family member or physician.

9. TRIAL ASSESSMENTS AND PROCEDURES

Trial assessments and procedures and their timing are summarized in the SoA (Section 1.7, Table 3, Table 4). Protocol waivers or exemptions for scheduled assessments and procedures are not allowed. No trial assessments or procedures may be conducted before the participant provides written informed consent.

9.1. Clinical Assessments

9.1.1. Demographic and Contact Information

Trial staff will obtain information on demographic characteristics (age, full date of birth, sex, place of birth, occupation) during screening along with contact information, including location of residence, participant's phone number(s), and names and phone numbers of any family/friends who can be contacted by trial staff in the event of emergency or when the participant is not able to be located. Identifying and location information will be kept at the trial sites only; it will not be entered into the trial database.

9.1.2. Medical and Treatment History

During the Screening Phase, the Investigator will collect a medical and treatment history to assess eligibility, including prior TB history, other health conditions, medications used, and allergies. During screening, participants will be specifically asked if they have ever received a COVID-19 vaccination regardless of when it was received due to the importance of COVID-19 as a potential comorbidity during this trial.

9.1.3. Review of Systems Including TB Signs and Symptoms

Review of Systems

A review of systems focused on common symptoms experienced during TB treatment and aligned with the safety profiles of the trial medications will be conducted at screening and every subsequent scheduled trial visit. The Investigator will evaluate the information gathered from the review of systems, and the interval medical history to determine whether an AE should be reported (see Section 10.1).

TB Signs and Symptoms

TB signs and symptoms will be assessed by the Investigator at the Screening Visit to assess eligibility (see Section 6.1). From the Baseline Visit (Visit 2) onward, a structured protocol-specific questionnaire (TB Signs and Symptoms Questionnaire) will be utilized that includes the WHO 4-symptom TB screen and questions focused on cough frequency and characteristics, impact of cough on daily activities, and other symptoms of chronic pulmonary conditions. TB signs and symptoms will also be assessed through vital signs (Section 9.1.7), physical examination (Section 9.1.8), laboratory tests (Section 9.2), and chest radiographs (Section 9.4.1).

9.1.4. Adverse Event Assessment and Follow-Up

Adverse events (AEs) will be detected through medical histories, review of systems, and physical examinations conducted throughout the trial as well as through safety laboratory tests and

procedures. See Section 10.1.1 for the definitions of an AE, serious adverse event (SAE), and adverse event of special interest (AESI) to be used in this trial. Investigators must proactively follow up previously identified AEs at subsequent visits. AEs must be followed until the end of the trial if not resolved; SAEs and non-serious AESIs must continue to be followed until resolved or stabilized even if follow-up extends beyond the end of a participant's trial participation. See Section 10 for details of AE, SAE, and AESI assessment, reporting, grading, causality assessment, follow-up, and outcome classification.

9.1.5. Adherence Assessment and Support

See Section 7.4 for details of assessing adherence to trial medications. Additional adherence support interventions will be made available to participants found to have adherence challenges. Examples of such interventions include, but are not limited to, psychosocial assessments, home visits by treatment support workers, referrals to peer support groups, or extra support during VOT sessions (see Trial Operations Manual for details).

9.1.6. Concomitant Medication Review

See Section 7.5 for details of reviewing and recording concomitant non-trial medications during the trial.

9.1.7. Vital Signs

Vital signs are to include temperature, respiratory rate (RR), heart rate (HR), blood pressure (BP), weight, and oxygen saturation, and all will be measured at every scheduled trial visit. Height will be measured once during screening. Body mass index will be calculated at every visit that weight is measured using the height measured at the screening visit. Oxygen saturation, RR, BP, and HR should be measured after the participant has been resting in the seated or supine position for ≥2 minutes. An out-of-range value may be repeated after ≥2 minutes of additional rest.

9.1.8. Physical Examination

During the screening period a full physical examination will be conducted as part of assessing participants' trial eligibility (eg, identifying important co-morbidities or evidence of extra-thoracic TB). After randomization at scheduled trial visits as well as poor treatment response and early termination visits (see Section 9.5.4 and Section 9.5.5), a focused physical examination will be performed as directed by the medical history and review of systems. Cardiopulmonary examination, including auscultation, should be included in all physical examinations. A focused physical examination may be conducted during an unscheduled trial visit at the discretion of the Investigator.

9.1.9. Visual Assessment

The Investigator or their delegate will conduct a fundoscopic examination during the initial screening physical examination. Investigators should refer participants with significant findings to an ophthalmologist for an evaluation to assist their determination of eligibility. Participants' visual acuity and color vision will be monitored at regular intervals during and after trial treatment to assess for possible signs of optic neuropathy toxicity from sutezolid (see Section 3.2.2.2.1) or ethambutol. Visual acuity will be assessed on each eye separately by means of a Snellen-type chart.

Color vision will be assessed on each eye separately using a validated screening tool administered by trial staff. See Section 7.6 for discontinuation recommendation for optic neuritis for participants taking sutezolid or ethambutol.

9.1.10. Peripheral Neuropathy Screening

Participants will be monitored at regular intervals during and after trial treatment for possible signs and symptoms of peripheral neuropathy from sutezolid (see Section 3.2.2.2.1) or isoniazid using the Brief Peripheral Neuropathy Screen (BPNS) test. The non-invasive BPNS test combines questions regarding neuropathic symptoms in the feet and lower legs with objective testing of ankle reflexes and vibration sensation in the big toes. See Section 7.6 for permitted dose modification of sutezolid for participants with evidence of peripheral neuropathy judged to be at least reasonably likely to be a toxic effect of sutezolid.

9.1.11. Functional Status Assessment

Participants' functional status will be assessed at screening for eligibility determination (see Section 6.2, exclusion criteria 12), at Weeks 9, 15, and 21, and at 12 months post-randomization using the Karnofsky Performance Status scale (National Cancer Institute, 2021).

9.1.12. Mid-upper Arm Circumference

Mid-upper arm circumference (MUAC) will be measured at baseline visit, Week 9, Week 17, Week 26, and Month 12 visits. MUAC will also be measured at visits conducted for suspected poor treatment response and early termination.

9.2. Laboratory Assessments

See SoAs in Table 3 and Table 4 in Section 1. for timing of all laboratory assessments. Details on blood/serum and urine collection procedures and on the laboratory tests to be performed are provided in the trial laboratory manual(s). See Section 9.3 for information on sputum collection and assessments.

9.2.1. Hematology

Blood will be drawn at screening for a complete blood count, including white blood cell count with differential, hemoglobin, and platelet count and repeated at regular intervals throughout the trial. Reticulocyte count will also be measured to monitor for signs of myelosuppression, which is a class effect of oxazolidinones to which sutezolid belongs, although myelosuppression has not been associated with sutezolid in nonclinical and clinical studies conducted to date (see Section 3.2.2.2.1).

9.2.2. Biochemistry

Blood will be drawn at screening for measurement of creatinine, blood urea nitrogen, potassium, sodium, chloride, serum bicarbonate, calcium, magnesium, ALT, AST, total and direct bilirubin, alkaline phosphatase, total protein, albumin, creatine kinase, lactate dehydrogenase, and C-reactive protein (CRP) and repeated at regular intervals throughout the trial. Estimated glomerular filtration rate will be calculated from serum creatinine.

9.2.3. HIV Testing

HIV testing will be conducted at screening for participants. Pre- and post-test counseling will also be provided with appropriate referral and linkage to HIV care and treatment facilities for participants that newly test positive. Trial staff should ask participants that report a medical history of HIV infection at screening to provide written documentation of their diagnosis. If written documentation is not available, HIV testing should be performed to confirm the diagnosis. Potential participants requiring HIV testing to determine eligibility who do not consent to be tested for HIV will not be eligible for the trial.

9.2.4. CD4 Testing

HIV-infected participants will have blood taken at screening for measurement of CD4 T-cell count for trial eligibility determination (see Section 6.2, exclusion criteria 9b) and, if randomized, at Week 26 and Month 12 visits. CD4 count should also be tested if a participant is being assessed for possible poor treatment response. Participants newly diagnosed with HIV during screening will not undergo CD4 testing as part of trial procedures because they will not be eligible for randomization due to the requirement of being on ≥3 months of antiretroviral treatment.

9.2.5. HIV Viral Load Testing

HIV-infected participants will have blood taken at screening for measurement of HIV viral load for trial eligibility determination (see Section 6.2, exclusion criteria 9c) and, if randomized, at Week 13, Week 26, Month 9, and Month 12 visits. Frequent HIV viral load testing has been incorporated to identify any clinical impact on viral suppression as a result of any potential drug-drug interactions. HIV viral load should also be tested if a participant is being assessed for possible poor treatment response. Participants newly diagnosed with HIV during screening will not undergo HIV viral load testing as part of trial procedures because they will not be eligible for randomization due to the requirement of being on ≥3 months of antiretroviral treatment.

9.2.6. Hepatitis B and C Testing

Blood will be taken at screening for testing of hepatitis B surface antigen and hepatitis C antibody for trial eligibility determination (see Section 6.2, exclusion criteria 15h and i).

9.2.7. Diabetes Screening

Blood will be taken at screening for hemoglobin A1c (HbA1c) measurement for trial eligibility determination (see Section 6.2, exclusion criteria 15g). Randomized participants whose screening HbA1c was ≥6.5% will have their HbA1c repeated at Week 26 and Month 12 visits.

9.2.8. Pregnancy Testing

Blood for serum beta human chorionic gonadotropin (β-hCG) will be collected from females of childbearing potential at the initial screening visit for trial eligibility determination (see Section 6.2, exclusion criteria 10). Point-of-care urine β-hCG testing will also be conducted at the baseline visit. After randomization, point-of-care urine or serum β-hCG testing will be conducted approximately every 3 to 4 weeks post-randomization at trial visits for all participants who are FOCBP until 12 weeks after last dose of trial drug.

9.2.10. Pharmacokinetic (PK) Sampling

Sparse PK sampling will be performed for all participants in the experimental arms only of both Stage 1 and 2. Population PK analysis will be used to analyze PK characteristics of delamanid and metabolite DM-6705, bedaquiline and its metabolite M2, OPC-167832, pretomanid, and sutezolid and its metabolite PNU-101603. PK analysis of key HIV antiretroviral medications (eg, dolutegravir) taken by HIV-infected participants will also be performed.

Details on plasma collection and processing procedures are provided in the Laboratory Manual.

For Stage 1, the following time points will be assessed for Arms 1 and 2:

- Baseline visit (Day 1) (to serve as predose sample), Week 1 (predose and 2 to 6 hours postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2 to 6 hours postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), Week 17

(predose), Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12 (18 samples per participant)

- Post-treatment random PK samples (Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12) will be tested for bedaquiline and its metabolite only.
- If a participant undergoes an Early Termination visit while they are on trial treatment, samples for PK should be collected. Ideally, predose and 2 to 6-hour postdose samples should be collected, but a single random sample is acceptable.

For Stage 2, Table 11 details the following time points that will be assessed for Arms 1 to 5 and the RR/MDR-TB cohort (18 samples per participant).

Table 11 Stage 2 Pharmacokinetic Sampling Time Points

XBOS Arm	Day 1	Week 1	Week 2	Week 4	Week 6	Week 9	Week 11	Week 13	Week 15	Week 17
1	Pre-dose	Predose and 2-6 hr postdose	Pre-dose	Pre-dose	Pre-dose	Predose & 2-6 hr postdose	Random	Random	Random	Random
2	Pre-dose	Predose and 2-6 hr postdose	Pre-dose	Pre-dose	Pre-dose	Predose & 2-6 hr postdose	Pre-dose	Random	Random	Random
3	Pre-dose	Predose and 2-6 hr postdose	Pre-dose	Pre-dose	Pre-dose	Predose & 2-6 hr postdose	Pre-dose	Pre-dose	Random	Random
4	Pre-dose	Predose and 2-6 hr postdose	Pre-dose	Pre-dose	Pre-dose	Predose & 2-6 hr postdose	Pre-dose	Pre-dose	Pre-dose	Random
5	Pre-dose	Predose and 2-6 hr postdose	Pre-dose	Pre-dose	Pre-dose	Predose & 2-6 hr postdose	Pre-dose	Pre-dose	Pre-dose	Pre-dose
RR/MDR-TB cohort	Pre-dose	Predose and 2-6 hr postdose	Pre-dose	Pre-dose	Pre-dose	Predose & 2-6 hr postdose	Pre-dose	Pre-dose	Pre-dose	Pre-dose
XBOS Arm	**Week 19**	**Week 21**			**Week 23**	**Week 26**	**Month 9**		**Month 12**	
1-5	Random	Random			Random	Random	Random		Random	
RR/MDR-TB cohort	Random	Random			Random	Random	Random		Random	

The predose blood draw should be drawn approximately 15 minutes prior to the daily dose of DBOS or PBOS except for the Day 1 predose blood draw, which may be taken at any time during the Baseline Visit before the first study treatment administration. The postdose blood draw should be done at a flexible time approximately 2 to 6 hours postdose. If a PK blood sample cannot be drawn at the designated time, a window of ±15 minutes for each blood draw is acceptable, with the exact time recorded. Post-treatment random PK samples will be collected and tested for bedaquiline and its metabolite only.

A separate modeling analysis plan will describe the population PK analysis. Results from the population PK analysis will be reported in a separate document (ie, not in the clinical study report).

Remaining samples collected for PK analysis may also be used for [redacted] after completion of the trial.

9.2.11. Pharmacodynamics Assessments

The PK/PD and/or exposure-response analysis may be used to investigate the relationship of delamanid, bedaquiline, sutezolid, pretomanid, OPC-167832, and the plasma exposure of their active metabolites with the efficacy and safety endpoints, as applicable.

The relationship between PK/PD data and efficacy endpoints, including, but not limited to [redacted]

A separate modeling analysis plan will describe the PK/PD analysis. Results from the PK/PD analysis will be reported in a separate document (ie, not in the clinical study report).

9.2.12. Pharmacogenomic Sampling

During the initial informed consent process, participants will be asked to provide consent for collection of a blood sample for pharmacogenetic analysis to look for genetic determinants of variability in drug metabolism of DBOS and PBOS agents between participants. Participants that do not provide consent for collection of a sample for pharmacogenetic analysis will continue to remain eligible to participate in the trial.

9.2.13. Urine Testing

Urine will be collected at screening for urinalysis (dipstick and reflex microscopy) and urine drug screen for trial eligibility determination (see Section 6.2). Urine dipstick will test for pH, specific gravity, glucose, protein, blood, leukocyte esterase, nitrites, ketones, bilirubin, and urobilinogen. Microscopic examination for red blood cells, white blood cells, casts, bacteria, and other abnormalities will be performed if urine dipstick is positive for protein, blood, leukocyte esterase, or nitrites or if otherwise indicated. Urine drug screen may include testing for cannabinoids, amphetamines, methamphetamines, cocaine, opiates, benzodiazepines, methaqualone, barbiturates, and phencyclidine based on assays available in trial countries. Urine will be collected for urine INH testing at Weeks 4, 9, 13, 17, 21, and 26 for participants randomized to 2HRZE/4HR (Arm 3 of Stage 1, Arm 6 of Stage 2) to confirm adherence. [redacted]

9.2.14. SARS-CoV-2 Testing

Identification of SARS-CoV-2 infection is important because acute COVID-19 symptoms and post-acute COVID-19 syndrome (PACS) might be confused with TB treatment failure, and active SARS-CoV-2 infection requires appropriate infection prevention and control measures within the trial sites (see Section 13.2.3). Active SARS-CoV-2 infection (defined as a positive PCR assay for SARS-CoV-2 on a nasopharyngeal or oropharyngeal swab) identified during the screening period

will exclude a participant from the trial (See Section 6.2, exclusion criteria 14). Active SARS-CoV-2 infection detected after randomization will not result in discontinuation of a participant from trial treatment or the trial unless an Investigator determines it is necessary due to the severity of their COVID-19 illness (see Section 8.3.2).

A nasopharyngeal or oropharyngeal swab for SARS-CoV-2 RT-PCR testing will be collected during screening for eligibility determination (see Section 6.2, exclusion criteria 14). It will also be performed at suspected poor treatment response (see Section 9.5.4) and early termination visits (see Section 9.5.5) unless the reason for an early termination is pregnancy or withdrawal of consent. SARS-CoV-2 RT-PCR testing can also be performed at any time an Investigator suspects COVID-19 infection or if a participant is a contact of a confirmed COVID-19 case.

9.2.15. Laboratory Specimen Collection, Preparation, Handling, Shipping, and Storage

All sample information regarding specimen collection, preparation, handling, and storage will be performed according to procedures specified in the trial-related Laboratory Manual(s). Specimens will be labelled with participant identification numbers, not names. Shipping will be performed in compliance with local and international regulations. Samples will be stored according to local regulations at a facility selected by the Sponsor. Samples will be kept for a maximum of 10 years from the end of the trial.

9.3. Sputum Assessments

Sputum will be collected to determine eligibility for the trial during screening, as well as at baseline and throughout the treatment and follow-up periods as outlined in Section 1.7, Table 3, Table 4. Instructions for sputum collection are provided in the Laboratory Manual. To ensure a high-quality specimen, each collection attempt should be preceded by patient education on proper sputum collection.

9.3.1. Screening Sputum for Eligibility

In Stage 1, a spot sputum will be collected during the screening period and tested using fluorescent smear microscopy and molecular test(s) (eg, line probe assay [LPA], [redacted]). Eligibility is confirmed if:

- Either smear is AFB-positive at a grade of ≥1+ as defined on the IUATLD/WHO scale or Xpert Ultra result demonstrates Mtb detected with a semi-quantitative result of ‘medium’ or ‘high’ on the sputum specimen collected for trial screening, AND
- Results from any combination of LPA, Xpert Ultra, or Xpert MTB/XDR do not detect resistance to INH and RIF.

In Stage 2, DS-TB participants will be confirmed as described for Stage 1. For participants with suspected RR/MDR-TB, a spot sputum will be collected at the first screening visit and tested using fluorescent smear microscopy and molecular test(s) (eg, LPA, Xpert Ultra, Xpert MTB/XDR). Eligibility is confirmed if:

- Either smear is AFB-positive at a grade of ≥1+ as defined on the IUATLD/WHO scale or Xpert Ultra result demonstrates Mtb detected with a semi-quantitative result of 'medium' or 'high' on the sputum specimen collected for trial screening, AND
- Results from any combination of LPA, Xpert Ultra, or Xpert MTB/XDR detect resistance to RIF (± INH), AND
- Results from any combination of LPA and/or Xpert MTB/XDR do not detect resistance to fluoroquinolones

In both stages, if testing is inconclusive from the first screening sputum specimen, a second sputum can be collected during the screening period. Screening sputum testing details are provided in the Laboratory Manual.

9.3.2. Sputum Assessments for Microbiological Response

At the baseline visit, three spot sputum specimens will be collected before the first dose of study treatment is administered. From Week 1 onwards, up to three sputum specimens will be collected according to Section 1.7, Table 3, Table 4, including a first-morning sputum and two spot sputum specimens. One spot sputum specimen at each of these visits may be reserved for the [redacted]
See Laboratory Manual for more details.

If a patient is unable to spontaneously expectorate a sputum sample, an attempt can be made to induce sputum production according to trial sites' local protocols for sputum induction. If sputum is still unobtainable, a specimen collection can be obtained at any time in the subsequent 48 hours post visit. A sputum sample will be defined as unobtainable if no sputum can be obtained during this 48-hour period. However, sputum induction cannot be used to collect sputum samples collected [redacted]

Each sputum specimen from the baseline visit onward will be tested with the following assays:

	Sputum 1	Sputum 2	Sputum 3
Standard assays	• Smear • Xpert Ultra • MGIT liquid culture • Solid culture	• Smear • Xpert Ultra • MGIT liquid culture • Solid culture	• None
Exploratory assays	[redacted]		
Comments	• Early morning preferred	• Spot	• Spot, cannot be induced • Collected in RNA preservation media
[redacted]			

The trial Laboratory Manual specifies the prioritization of sputum tests in the case of limited sputum samples and/or volume. Mycobacterial cultures will be identified by methodologies specified in the Laboratory Manual. Results from MGIT liquid culture and solid culture will be combined for the microbiologic component of the primary efficacy endpoint.

9.3.3. Drug Susceptibility Testing (DST)

Phenotypic DST will be performed on the baseline visit or Week 1 sputum culture depending on suitability of culture growth for DST performance. In Stage 1, DST will also be performed on the first culture positive for Mtb at Week 13 or afterwards in all arms. In Stage 2, DST will also be performed on the first culture positive for Mtb at Week 9 or afterwards for Arm 1, Week 11 or afterwards for Arm 2, and Week 13 or afterwards for Arms 3 to 6 and the RR/MDR-TB cohort. DST may be performed on additional cultures positive for Mtb if deemed pertinent by the Sponsor.

In Stage 1, phenotypic DST will be performed for all regimens to maintain the blinding of trial microbiology laboratory staff. Additional DST may be performed at the discretion of the Investigator and/or the Sponsor. In Stage 2, DST will be performed as in Stage 1, with the addition of DST to a fluroquinolone (specific fluoroquinolone tested may vary based on trial site) using the MGIT culture system for the RR/MDR-TB cohort.

9.3.4. Mtb Strain Genotyping

Mtb strain genotyping will be used to assist in the determination of whether a participant with a positive culture at the completion of treatment or after in the post-treatment follow-up period has relapsed or been re-infected with another strain of Mtb. Genotyping will be performed on a baseline culture (culture collected at baseline visit or, in rare cases, Week 1) and the first Mtb-positive culture occurring from the end of treatment study visit through the end of the post treatment follow-up period. In addition, the Sponsor may request genotyping at other time points as needed. Further details will be specified in the Laboratory Manual.

9.3.5. Storage of Mtb Isolates

Mtb isolates from cultures will be stored for confirmatory DST, future MIC testing, genetic characterization of Mtb, and potential assessment of [redacted].

9.3.6. Sputum Specimen Collection, Preparation, Handling, and Shipping

Specimen collection, preparation, and handling will be performed according to procedures specified in the Laboratory Manual. Participants will be educated specifically on how to safely collect sputum specimens at home to minimize risk to others in the home/community. Shipping will be performed according to the Laboratory Manual and in compliance with local and international regulations.

9.4. Other Procedures

9.4.1. Chest X-Rays (CXRs)

To assess participant eligibility, a good quality posterior-anterior (PA) CXR will be obtained during the screening period (see Section 6.1, inclusion criteria 4e). A recently conducted CXR (eg,

within 1 week prior to screening) may be used for eligibility determination if the digital CXR file is available.

Post-randomization PA CXRs will be performed at Weeks 4, 9, 17, and 26 and Month 12. Unscheduled PA CXRs should be performed in participants being assessed for possible poor treatment response (Section 9.5.4) and at early termination visits (Section 9.5.5) if a participant is being withdrawn from the trial due to treatment failure. [redacted]

Investigators are permitted to use artificial intelligence-based computer-aided X-ray interpretation programs and/or radiologists' interpretations to assist them with their CXR interpretations.

9.4.2. Electrocardiograms (ECGs)

Twelve-lead ECGs will be performed at screening for all participants as part of their eligibility assessment (see Section 6.2, exclusion criteria 17). Randomized participants in both stages will have ECGs performed regularly until approximately 2 months post-treatment. The primary purpose of ECG collection is to monitor for significant prolongation in the QTcF interval due to bedaquiline and/or delamanid. ECGs will be performed in triplicate and centrally read by cardiologists.

9.4.3. Spirometry

Spirometry will be performed at baseline, Week 9, Week 17, Week 26, and Month 12 with specific focus on measurement of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Spirometry should be attempted to be performed at poor treatment response visit (Section 9.5.4) as well as early termination visit (Section 9.5.5) for any participant withdrawn due to suspected or confirmed TB treatment failure and/or disease relapse.
[redacted]

Detailed procedures for conducting spirometry, including recommended infection prevention and control measures for TB and COVID-19, are detailed in the Trial Operations Manual. If a site is unable to implement sufficient infection prevention and control measures to ensure the safe conduct of spirometry, omitted spirometry assessments will not be considered protocol deviations.

[redacted]

[redacted]

9.5. Trial Schedule

Details on the schedule of assessments and procedures unique to the Screening Period, Treatment Period, Follow-Up Period, Possible Poor Treatment Response Visit, and Early Termination Visit are provided in Section 1.7, Table 3, Table 4. More detailed description of the assessments and procedures are found in Section 9.1, Section 9.2, Section 9.3, and Section 9.4. Selected important periods and visits are highlighted here in the sub-sections that follow.

9.5.1. Screening Period

9.5.1.1. Initial Screening Visit

The following activities will be conducted after informed consent is obtained during the screening period lasting up to 10 days:

- Assessment of inclusion and exclusion criteria
- Collection of demographic and contact information
- Interview for medical history, including TB treatment history
- Review of systems, including TB signs and symptoms
- Concomitant medication review inclusive of the 30-day period prior to informed consent
- Vital signs, including height
- Complete physical examination
- Functional status assessment using Karnofsky performance scale
- Spot sputum sample for microbiologic eligibility determination (see Section 6.1 and Section 9.3.1) – a second spot sputum sample may be collected if initial results are inconclusive
- Blood draw for CBC and WBC differential, reticulocyte count, electrolytes, renal function tests, liver enzymes, bilirubin, lactate dehydrogenase, creatine kinase, C-reactive protein (CRP), hemoglobin A1c, hepatitis B surface antigen, hepatitis C antibody, and serum β-hCG for pregnancy testing if participant is a FOCBP
- HIV testing will be performed if one or more of the following apply: a) HIV status is unknown or last HIV test was negative or b) written documentation of HIV infection is not available for confirmation of HIV-infected status
- If known to be HIV-infected and already taking ART for ≥3 months, blood for CD4+ T-cell count and HIV viral load will also be collected unless results are available for tests performed within 30 days prior to informed consent
- Nasopharyngeal or oropharyngeal swab for SARS-CoV-2 PCR
- Urine sample collection for urinalysis and urine drug screen
- PA CXR
- 12-lead ECG

9.5.1.2. Baseline Visit (Day 1)

Eligibility for randomization will be based on the inclusion and exclusion criteria described in Sections 6.1 and Section 6.2. Participants found to be eligible for the trial will be invited for a baseline visit during which the following assessment and procedures will be performed:

- Review and confirmation of inclusion and exclusion criteria
- Review of systems, including TB signs and symptoms
- Interval medical history
- Focused physical examination
- Mid-upper arm circumference
- Adverse event review
- Concomitant medication review
- Visual acuity and color vision screenings
- Peripheral neuropathy screening
- [redacted]
- Blood collection for sparse PK [redacted]
- Blood collection for pharmacogenetic testing only for those participants providing specific consent for it (Section 9.2.12)
- Urine collection for point-of-care β-hCG for pregnancy testing if participant is a FOCBP [redacted]
- Spirometry
- [redacted]

Randomization and dispensing of trial treatment will occur after the Investigator has confirmed a participant's eligibility. Day 1 is defined by the first day a participant takes trial treatment. Other baseline visit procedures may be done before the first day of trial treatment administration. Trial sites will maintain a screening log to record details of all participants screened, to confirm eligibility or record reasons for screening failure, as applicable.

9.5.2. Treatment Period (Visits from Week 1 through End of Treatment)

Trial visits should be conducted within a window of ±4 days. In summary, safety assessments will regularly be conducted, including vital signs, focused physical examinations, interval medical history and review of systems (including TB signs and symptoms) with a focus on adverse events, ECGs, safety laboratory tests, and visual and peripheral neuropathy screens. Concomitant medications will be reviewed, and an assessment of adherence done at every visit. Treatment efficacy will be closely monitored with approximately 15 sputum samples per participant collected from baseline through Week 26. Additional procedures for treatment monitoring and [redacted]

Telephonic and/or home visits in lieu may be permitted after discussion with the Sponsor in circumstances where participants are unable to travel to the trial site for a scheduled visit, such as COVID-19 travel restrictions or requirements for quarantining or isolation.

9.5.3. Follow-Up Period

Trial visits after Week 28 should be conducted within a window of ±7 days. In summary, these visits focus on monitoring participants closely for signs and symptoms of possible recurrent TB through clinical evaluations and continuation of sputum collection for microbiologic assessments regardless of symptoms as well as review of adverse events and concomitant medications. In Stage 1, DST will be performed on the first culture positive for Mtb collected at Week 13 or afterwards for comparison with the baseline DST results. In Stage 2, DST will be performed on the first culture positive for Mtb at Week 9 or afterwards for Arm 1, Week 11 or afterwards for Arm 2, and Week 13 or afterwards for Arms 3 to 6 and the RR/MDR-TB cohort.

Mtb strain genotyping will be performed on the first positive culture for Mtb collected from the end of treatment study visit through the end of the post treatment follow-up period for comparison with strain genotyping results from baseline. This comparison will assist in the determination of whether a participant with a positive Mtb culture at the end of treatment or after has relapsed or been re-infected with Mtb. Strain genotyping and/or DST may be conducted on other positive cultures in the follow-up period as needed.

Adverse events will continue to be assessed during this period to document their final outcomes. Concomitant medications will be reviewed at each trial visit in this period. ECGs and vision and peripheral neuropathy screens will extend into the early post-treatment follow-up period to track the trajectory of any study drug toxicities after treatment completion. Spirometry and CXRs will also be conducted during the post-treatment follow-up period to assess their evolution after treatment completion.

Telephonic and/or home visits may be permitted after discussion with the Sponsor in circumstances where participants are unable to travel to the trial site for a scheduled visit, such as COVID-19 travel restrictions or requirements for quarantining or isolation.

9.5.4. Procedures for Participant With Suspected or Confirmed Poor Treatment Response

Investigators may identify a participant with a possible or confirmed poor treatment response through various methods, including clinical evaluations (eg, new or worsening cough or other TB symptoms), microbiologic results (eg, smear and/or culture reversion to positive after previous conversion to negative), laboratory tests, CXR findings, or a combination of these methods. A possible or confirmed poor treatment response may be identified while a participant is still taking their trial treatment (ie, treatment failure) or in the follow-up period after completing treatment (ie, post-treatment relapse).

When a participant with a possible or confirmed poor treatment response is identified, a poor treatment response (PTR) visit should be initiated, and the following investigations should be

conducted even if they are not part of the regularly scheduled assessments and procedures for the scheduled trial visit:

- Vital signs
- Interval medical history
- Review of systems, including TB signs and symptoms
- AE review
- Mid-upper arm circumference
- Concomitant medication review
- Focused physical examination
- Functional status assessment
- Blood draw for CBC with WBC differential, biochemistry, CRP, CD4 count and HIV viral load for HIV-infected participants, [redacted]
- [redacted]
- Respiratory sample for SARS-CoV-2 PCR
- PA CXR
- Spirometry
- [redacted]
- Up to three sputum samples. At least one of the samples should be a first morning specimen, if possible. The third sample should be collected [redacted]. Samples can be collected over a period of up to 1 week.

If a participant is identified to have a potential or confirmed poor treatment response between their regularly scheduled trial visits (eg, based on a positive sputum culture result received between visits), the Investigator may either conduct the PTR visit at the participant's next scheduled visit or ask the participant to return earlier for an unscheduled visit.

If, after assessing a participant with possible or confirmed poor treatment response, an Investigator wants to permanently stop or change a participant's trial treatment or restart TB treatment in the follow-up period, the STrAW Concilium will be consulted for review of the participant's clinical status. TB treatment should not be permanently changed, stopped, or restarted before consultations with the STrAW Concilium have been completed if the participant's clinical condition permits (Section 1.6).

After a participant has been determined by the Investigator to have relapsed TB in the post-treatment follow-up period, a fourth [redacted] should be performed if the participant has previously consented to undergo [redacted] Stage 2 only; see Section 9.4.4).

Investigators should follow local TB treatment guidelines when prescribing treatment for participants determined to have failed trial treatment or experienced a TB relapse (or re-infection). Participants that have failed trial treatment or experienced a relapse/re-infection and the Investigator prescribes HRZE for further treatment of their TB can receive the HRZE medications through the trial. Sites should ensure that these participants are successfully linked to an appropriate local TB treatment center for ongoing treatment when possible. These participants should also undergo an early termination visit (see Section 9.5.5).

9.5.5. Early Termination Visit

Any participant withdrawn from the trial before their last scheduled trial visit will be asked to return for an early termination visit. Assessments to be conducted at the early termination visit are specified in Table 3 and Table 4 in Section 1.7. Participants with ongoing AEs at the time of the early termination visit should be followed up until the AEs have resolved or stabilized.

9.5.6. Follow-Up After Permanent Discontinuation of Trial Treatment

Participants whose trial treatment is permanently discontinued should continue to be followed in the trial through 12 months post randomization for outcome determination unless consent for on-going trial participation is withdrawn at which time an early termination visit should be conducted. If a participant is discontinued from the assigned treatment prior to its completion, they will be asked to return at the trial visit week that corresponds to their assigned trial treatment duration (eg, Week 17 visit for DBOS and PBOS arms in Stage 1) as well as for the Week 26 and Month 12 visits. If a participant is withdrawn from the trial between Week 26 and Month 12, they will be asked to return for the Month 12 post randomization visit. The following assessments should be completed at post-treatment discontinuation follow-up visits, if possible:

- Interval medical history, including review of any ongoing AEs identified at last trial visit
- Review of systems, including TB signs and symptoms
- Mid-upper arm circumference
- Concomitant medication review
- Vital signs
- Focused physical examination
- Visual assessment
- Peripheral neuropathy screen
- Functional status assessment
- [redacted]). Samples can be collected over a period of up to 1 week.
- Blood draw for CBC with WBC differential, reticulocyte count, biochemistry, creatine kinase, LDH, CRP, CD4 count and HIV viral load for HIV-infected participants, PK measurements, [redacted]
- [redacted]
- Urine pregnancy test for FOCBP
- Respiratory sample for SARS-CoV-2 PCR if symptoms of possible COVID-19 are present
- PA CXR if TB signs or symptoms are present and/or Investigator suspects possible TB
- Standard 12-Lead ECG
- Spirometry

9.5.7. Missed Trial Visit

A visit is recorded as missed if it does not occur within the specified time windows on the SoA for Stage 1 and Stage 2. Sites should attempt to collect sputum samples within the allowable trial visit

time window even if the full visit cannot be conducted. If the sputum samples cannot be collected within a trial visit time window, the Investigator may consult the Sponsor to determine if sputum should still be collected.

9.5.8. Unscheduled Trial Visit

An unscheduled visit refers to an additional trial visit performed for a participant by the trial site beyond those specified in the SoAs (Section 1.7, Table 3, Table 4). The most common reasons anticipated for unscheduled trial visits are participants presenting with new symptoms/AEs between scheduled trial visits, follow-up of abnormal clinical safety lab test results, and need for collecting additional sputum samples if previous culture results are contaminated (particularly for key visits such as end of treatment and end of trial visits). Assessments and procedures conducted during an unscheduled visit will be at the discretion of the Investigator in consultation with the medical monitor.

10. ASSESSMENT OF SAFETY AND MANAGEMENT OF ADVERSE EVENTS

Urgent safety concerns where a trial participant's well-being is imminently threatened should immediately be discussed with the Sponsor and/or CRO upon occurrence or awareness by the Investigator.

Adherence to the requirements of the trial protocol, including those specified in the SoA (Section 1.7, Table 3, Table 4) is essential for monitoring and protecting participants' well-being, and is required for trial conduct.

Safety outcomes will include AE, AESI, and SAE and are described in Section 10.1.

10.1. Adverse Events, Adverse Events of Special Interest, Adverse Reactions, and Serious Adverse Events

10.1.1. Definitions

10.1.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial participant, temporally associated with the use of trial intervention, whether or not it is considered related to the trial intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of trial intervention.

The following events meet the definition of an AE:

- Any abnormal laboratory test result (eg, hematology, clinical chemistry, or urinalysis) or other safety assessment (eg, ECG, radiologic scans, vital sign measurements, visual assessment), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator
- Exacerbation of a chronic or intermittent pre-existing condition, including an increase in frequency of signs, symptoms, and/or intensity of the condition
- New conditions detected or diagnosed after trial start even though it may have been present before the start of the trial
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial intervention or a concomitant medication
    - An overdose by itself without any signs and symptoms will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

The following events will not be considered an AE:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of a pre-existing disease or condition that was present or detected at the start of the trial, which do not constitute a clinically significant worsening in the medical judgement of the Investigator
- Lack of efficacy of the trial treatment; these instances will be captured in the efficacy outcome measures

10.1.1.2. Adverse Drug Reaction

An adverse drug reaction (ADR), or adverse reaction, refers to a noxious and unintended response to a medicinal product regardless of the dose administered. It can also be the result of an overdose, misuse, or abuse of a medicine. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (ie, a possible relationship cannot be ruled out).

When an adverse event is judged to be serious (see definition below) and related to an investigational product, it is referred to as a serious ADR and is subject to expedited reporting (see Section 10.1.9).

10.1.1.3. Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:

a) Results in death
b) Is immediately life-threatening
   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.
c) Requires inpatient hospitalization or prolongation of an existing hospitalization

   Note: In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether a hospitalization occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Hospitalization for social or economic reasons is also not considered an AE.

d) Results in persistent or significant disability or incapacity

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly or birth defect
f) Is a medically significant or important event or reaction

Note: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.1.1.4. Adverse Event of Special Interest

Adverse events of special interest (AESIs) are adverse events that the Sponsor wants to monitor carefully and are subject to expedited reporting (within 24 hours) following the same process and timelines of SAEs. In this trial, the following AEs will be collected and reported as AESIs, even if they do not meet the SAE definition:

- Hepatotoxicity, as defined by all the following:
  - Elevated ALT or AST >3x ULN,
  - Elevated total bilirubin >2x ULN,
  - No evidence of cholestasis, and
  - No reasonable alternative explanation than drug-induced liver injury for the elevation in ALT/AST and total bilirubin, such as viral hepatitis
- Peripheral neuropathy of severity Grade 3 or above
- Optic neuritis confirmed by an ophthalmologist
- Grade 3 or above anemia, leukopenia, or thrombocytopenia
- QTcF interval prolongation >500 msec or a clinically significant cardiac arrhythmia associated with QT prolongation, such as Torsades de pointes or polymorphic ventricular tachycardia

The Investigator is responsible for following up AE that are serious, considered related to the trial intervention or trial procedures, or that caused the participant to discontinue the trial.

10.1.2. Time Period for Collecting AE Information

AEs will be collected from the time each participant has signed the ICF until they have completed the last follow-up visit or ET visit. Participants with SAEs and AESIs that are still ongoing at the time they exit the trial – either from early withdrawal, or at the end of the trial at Month 12 post-randomization should continue to be followed until the SAE or AESI has resolved or reached a stable outcome.

An Investigator is not obligated to actively seek information on new or ongoing AEs after conclusion of trial participation. However, if an Investigator learns of any new SAE, including a death, at any time after a participant has been discharged from the trial, and they consider the event to be related to the trial intervention or trial participation, the Investigator must promptly notify the Sponsor.

10.1.3. Methods of Detection of AE

Trial nurses and physicians will collect and document information and events that would potentially meet the definition of an AE at every trial visit. Participants will be asked about specific symptoms (eg, details about TB symptoms and common AEs), new diagnoses, and hospitalizations. In addition, open-ended, non-leading questions will be asked to gather information on potential AEs that could be otherwise missed. ECGs, visual assessments, and peripheral neuropathy screens will also be performed at regular intervals to identify possible AEs. Safety laboratory tests will be monitored as detailed in Table 3 and Table 4 in Section 1.7. Results of laboratory investigations should be recorded as adverse events only if determined to be clinically significant by an Investigator.

After reviewing potential AEs identified from these various methods, Investigators will determine if an event meets AE criteria and then assess the intensity/grading (Section 10.1.5), causality (Section 10.1.6), and seriousness (Section 10.1.1.3) of events classified as AEs. Investigators should perform additional evaluations as medically indicated to elucidate the nature and/or causality of the AE as fully as possible. This may include additional laboratory tests, histopathological examinations, or consultation with specialists.

The trial team will proactively follow up AE events after their initial reporting at a participant's subsequent visits/contacts. All AE will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3).

10.1.4. Recording of AE

When an AE occurs, it is the responsibility of the Investigator to review all available documentation (eg, clinic notes, hospital progress notes, laboratory reports, and diagnostics reports) related to the event and record all relevant information, such as onset and resolution dates and actions taken in response to the event, in the appropriate section of the CRF. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, other clinical information, and available lab results. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE using a recognized medical term or diagnosis that accurately reflects the event.

10.1.5. Grading Intensity (severity) of AE

Clinical signs, symptoms, and diagnoses that constitute an AE will be classified by an Investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life threatening (Grade 4). All deaths related to an AE will be classified as Grade 5.

Grading criteria reported in the Division of Allergy and Infectious Diseases (DAIDS) may help in the assessment of intensity of AEs. However, an Investigator is not obliged to follow these criteria

and their own medical judgement should prevail. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE (see Section 10.1.1.3), not when it is rated as severe.

10.1.6. Assessment of Causality of AE

Each AE will be assessed to determine the likely causality between trial medications and the AE. Careful medical judgement should be exercised to determine the level of causal relationship. The causality assessment will be determined by the Investigator using a two-level scale: related or not related and will be conducted for each medication in the trial regimen (ie, causality with the AE will be assigned separately for each trial medication, not the regimen as a whole).

An AE is considered related to a trial medication if there is a reasonable possibility that the medication contributed to the AE. Not related means there is no reasonable possibility that the AE is causally related to administration of the trial medication and that there is a more likely alternative cause for the AE, such as an underlying disease, concomitant treatment, and other risk factors, as well as the temporal relationship of the event to trial medication administration.

An Investigator may change their assessment of causality based on new information obtained and update the appropriate participant trial documents. The causality assessment is one of the criteria used when determining regulatory reporting requirements (see Section 10.1.9).

Trial SAE and AESI reporting forms will also permit the Investigator to assign their judgement of causality for current concomitant medications at the time of the event and any recent time-sensitive vaccinations administered with specific focus on recent SARS-CoV-2 vaccinations.

The Sponsor or designee will have the opportunity to confirm the seriousness and causality based on the clinical judgement of the medical monitor and Sponsor designee. If a SAE is considered unrelated by the Investigator but the Sponsor believes that there is a reasonable possibility that the event is related, the Sponsor will upgrade the case to a 'related' status. The Sponsor or designee will never downgrade a case from serious to non-serious or related to not related.

10.1.7. Assessment of SAE Expectedness

Each SAE will be evaluated by the Sponsor based on applicable product information (Investigator Brochures for OPC-167832 and sutezolid and package inserts/Investigator Brochures for delamanid, bedaquiline, pretomanid). For the 2HRZE/4HR arm, each SAE will be evaluated based on applicable product information available for the fixed dose combination (eg, Rifafour® e275 HRZE) or package inserts for the individual component drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) that is approved and marketed in the given trial country and administered per the national TB treatment guidelines applicable for that country.

Expected adverse events are those consistent with the applicable product information provided by the Sponsor.

10.1.8. Assessment of AE Outcome

The outcome of each AE will be reported, even if this extends after the final trial visit for SAEs and AESIs. AE outcomes will be classified as one of the following:

- Resolved
- Resolved with sequelae
- Ongoing
- Death

An AE will be considered resolved when a participant's condition returns to normal or their baseline status as established during the screening period. Resolved with sequelae indicates the condition has stabilized with the expectation that it will remain chronic or the event is resolved but left the participant with a long-lasting or permanent symptom or sign.

If the event has not resolved by the final trial visit, it will be documented as 'ongoing' though SAEs and AESIs must continue to be followed until resolved or stabilized.

10.1.9. Reporting Requirements for SAE, Serious ADR, AESI, and Other Events

All SAE (including serious ADR and deaths) and AESI will be reported to the Sponsor or designee within 24 hours. Any updated SAE or AESI clinical information or data will be submitted to the Sponsor or designee within 24 hours of it being available. Prompt notification is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the trial interventions under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and potentially other regulatory agencies about the safety of the trial intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators. The Sponsor also has safety reporting obligations to the respective manufacturers of bedaquiline, delamanid, pretomanid, OPC-167832, and sutezolid through individual safety and data exchange agreements with each manufacturer.

All fatal and life-threatening serious unexpected ADR are to be reported to the applicable health authorities within 7 calendar days after first knowledge with a complete report to be submitted within an additional 8 calendar days. Suspected, unexpected serious ADRs (SUSAR) that are not fatal or life threatening are to be reported to these same authorities no later than 15 calendar days after first knowledge. An Investigator who receives a SUSAR report or other specific safety information (eg, summary or listing of SAEs/SADRs) from the Sponsor will review and file it, and notify their IRB/IEC, if required.

Certain events other than SAEs and ADRs require immediate reporting to the Sponsor. These include withdrawal of consent, protocol violation affecting safety, AE thought to be an allergic reaction to study drug, event precluding further administration of study drug in the Investigator's opinion, and pregnancy. Reporting of these events will be detailed in the Trial Operations Manual.

10.1.10. Death Events

Any untoward medical occurrence resulting in death is reported as SAE. Any event resulting in death without identification of medical occurrence must also be reported as SAE; such event will be coded as "death NOS" (No Other Specified") until the medical event is identified.

10.2. Management of Adverse Events

10.2.1. General AE Management Guidance

The following guidance applies to AEs that an Investigator judges may be due to one or more trial medications. It is general guidance, and the clinical judgement of Investigators should prevail if it conflicts with these recommendations.

<table>
<tr><th>Intensity/ Severity grading</th><th>General guidance for management approach when AE may be due to one or more trial medications</th></tr>
<tr><td>1
(mild)</td><td>• Monitor participant closely
• Continue trial medications
• Give appropriate concomitant medication(s) to manage symptoms only as needed</td></tr>
<tr><td>2[a]
(moderate)</td><td>• Monitor participant closely (additional unscheduled visits and investigations [eg, lab tests, ECG, etc.] may be indicated)
• Trial medications will generally be continued at the discretion of the Investigator. One or more trial medications may be held if the Investigator's judgement is that continuing them would be unsafe for participant
• Give appropriate concomitant medication(s) to manage symptoms only as needed</td></tr>
<tr><td>3[a]
(severe)</td><td rowspan="2">• Investigator should carefully assess participant to determine if there are other possible causes for the toxicity, such as a concomitant medication or exacerbation of underlying medical condition. Appropriate investigations should be conducted to investigate the etiology
• When possible, concomitant medications or co-morbidities suspected of causing the AE should be interrupted/managed first before withholding trial medications. Participant safety is always the top priority.
• When the Investigator's judgement is that one or more trial medications is at least possibly the cause of the AE then the suspected trial medication(s) may be temporarily interrupted
o When suspected trial medications are withheld as possible cause of a toxicity, appropriate investigations should be performed and repeated until the toxicity has resolved or stabilized.
o Trial medications should be resumed as soon as safely possible
o Investigators must consult the STrAW Concilium if they have judged that one or more trial medications should be permanently discontinued</td></tr>
<tr><td>4[a]
(potentially life-threatening)</td></tr>
<tr><td colspan="2">[a] The Investigator may consult the medical monitor and Sponsor for further input regarding the judgment of the likely cause of an AE and its management</td></tr>
</table>

10.2.2. Management of Trial Medication Overdose

In case of an overdose of one or more of the trial medications, appropriate medical treatment will be instituted, guided by an interim history, physical examination, and any procedures or investigations deemed appropriate by the treating Investigator. No specific treatments or antidotes are recommended, and hospitalization is not required. Management of the consequences of an overdose should follow the general guidance for the management of AEs provided above.

11. STATISTICAL CONSIDERATIONS

This section contains a summary of the statistical analyses to support the primary and secondary objectives of this trial.

Statistical analyses of safety and efficacy data will be performed using SAS software version 9.4 or higher, except for statistical modeling which may be performed using R. Statistical tests will be performed at the 2-sided 0.05 level of significance, and two-sided 95% confidence intervals will be presented, except where noted otherwise. Results from Stage 1 and Stage 2 of the trial will be summarized separately, and the last observation prior to the initiation of dosing on Day 1 of the trial will be used as baseline, except where noted otherwise.

11.1. Populations for Analysis

Table 12 defines the populations for purposes of the statistical analyses.

Table 12 Analysis Populations

Population	Description
Modified intention to treat (mITT) population	All participants randomly assigned to trial intervention, who received the trial intervention and have DS-TB that is confirmed as sputum culture positive at baseline. Participants will be analyzed according to the intervention to which they were randomized.
Per Protocol (PP) population	All participants randomly assigned to trial intervention, who received the trial intervention, have DS-TB that is confirmed as sputum culture positive at baseline, and did not substantially deviate from the protocol procedures. Participants will be analyzed according to the intervention they actually received.
Safety population	All participants randomly assigned to trial intervention, who received at least one dose of the trial intervention. Participants will be analyzed according to the intervention they actually received.
PK population	Participants with at least one quantified plasma PK sample
RR/MDR-TB population	Participants with RR/MDR-TB who are enrolled into the single-arm cohort, regardless of baseline sputum culture positivity, and receive at least one dose of the XBOS regimen.

11.2. Statistical Hypotheses

Stage 1 (Phase 2b)

All Stage 1 analyses will be descriptive; no formal hypothesis testing will be performed. The efficacy analyses will focus on unfavorable outcome status (definition in Section11.3.1) at the end of the treatment period and during treatment of each of DBOS and PBOS relative to that of 2HRZE/4HR. The choice of which experimental regimen (DBOS or PBOS) to consider for study in Stage 2 will be based on a comprehensive review of Stage 1 efficacy and safety results.

Stage 2 (Phase 2c)

Primary hypothesis: In the mITT population, for a range of XBOS regimen durations of 4 months or less, participants randomized to receive XBOS have model-estimated unfavorable outcome rates at 12 months post-randomization that are non-inferior to 2HRZE/4HR, based on a non-inferiority margin of 12 percentage points (see Section 11.7).

11.3. Primary and Key Secondary Endpoints

See Section 1.4 for table of trial objectives, endpoints, and estimands.

Stage 1

Safety

The primary safety endpoint is severe AEs (≥ Grade 3) and SAEs through the two weeks after the end of treatment (through 19 weeks for DBOS and PBOS and through 28 weeks for 2HRZE/4HR). The secondary safety endpoints are Grade 3 or higher AEs and SAEs through the end of the post treatment follow up period (12 months post randomization) and all-cause trial treatment discontinuation. The same safety endpoints will also be assessed in the subset of participants that are HIV-infected. Participants in all three randomization arms will also be assessed for safety at 12 months post randomization.

Efficacy

The primary efficacy endpoint is unfavorable outcome status through the end of treatment (through 17 weeks for DBOS and PBOS and through 26 weeks for 2HRZE/4HR). Please see Section 11.3.1 for the definition of unfavorable outcome.

Other key secondary efficacy endpoints include:

- Unfavorable outcome status at 12 months post-randomization;
- Unfavorable outcome status through end of treatment (through 17 weeks for DBOS and PBOS and through 26 weeks for 2HRZE/4HR) and at 12 months post randomization in the subset of participants with HIV co-infection in each treatment group;
- Unfavorable outcome status in all arms at 6 months after the randomized duration of trial treatment;
- Time to SCC to negative for Mtb growth in MGIT during the treatment period for all arms;
- TTD curves in MGIT for all 3 arms through 4, 8, 9, 13, and 17 weeks of treatment as calculated from the area under the TTD vs week curve (AUC);
- Sputum culture status for Mtb growth in MGIT at all time points at which sputum culture is assessed during the treatment period for all 3 arms;
- Time to sputum culture conversion to negative in solid culture during treatment period;
- Sputum culture conversion to negative for Mtb growth in solid culture at all time points at which sputum culture is assessed during treatment; and
- Emergence of resistance to the trial treatment drugs.

Stage 2

Safety

The primary safety endpoint is severe AEs (≥ Grade 3) and SAEs through two weeks after the end of treatment (through 11 to 19 weeks for XBOS depending on arm and through 28 weeks for 2HRZE/4HR).
The secondary safety endpoints are:

- Grade 3 or higher AEs and SAEs through the end of the post treatment follow-up period (12 months post randomization) in all DS-TB participants.

- All-cause trial treatment discontinuation.
- The same safety endpoints will be assessed at the end of treatment and the end of the post treatment follow-up period in the subset of DS-TB participants that are HIV-infected.
- The same safety endpoints will be assessed at the end of treatment and the end of the post treatment follow-up period in RR/MDR-TB participants.

Efficacy

The primary efficacy endpoint is unfavorable outcome status (see Section 11.3.1) at the end of post-treatment follow-up period (12 months post-randomization).
Key secondary efficacy endpoints include:

- Unfavorable outcome status at the end of treatment in the XBOS arms and 2HRZE/4HR;
- Unfavorable outcome status at the end of treatment and at the end of post-treatment follow-up period (12 months post-randomization) in the subset of participants with HIV co-infection in each arm;
- Unfavorable outcome status in all arms at 6 months after the randomized duration of trial treatment;
- Time to SCC in MGIT in each arm;
- TTD curves in MGIT in each arm through Weeks 4, 8, 9, 11, 13, 15, and 17 as calculated from the area under the TTD vs week curve (AUC);
- Sputum culture conversion to negative by 8 weeks and end of treatment in MGIT and solid culture;
- Sputum culture conversion to negative for Mtb growth in MGIT at all time points at which sputum culture is assessed during treatment period;
- Time to sputum culture conversion to negative in solid culture during treatment period;
- Sputum culture conversion to negative for Mtb growth in solid culture at all time points at which sputum culture is assessed during treatment period; and
- The emergence of resistance to the trial treatment drugs.

11.3.1. Definition of Unfavorable Outcome Status

Unfavorable outcome status will serve as the basis for assessment of the primary efficacy endpoint in both Stage 1 and Stage 2. Participants that experience one or more of the following events following randomization will be categorized as having an unfavorable outcome status:

- Absence of microbiological cure:
    - Stage 1
        - DBOS/PBOS: sputum culture positive at Week 17
        - 2HRZE/4HR: sputum culture positive at Week 17 or at any subsequent time point through Week 26
    - Stage 2
        - XBOS: sputum culture positive at end of assigned treatment duration visit
        - 2HRZE/4HR: sputum culture positive at Week 17 or at any subsequent time point through Week 26
        - RR/MDR-TB: sputum culture positive at Week 17
    - Positive culture must be with a Mtb strain indistinguishable from baseline.

- Death from any cause.
- Permanent discontinuation of trial treatment before the end of the assigned treatment duration for the following reasons: safety, tolerability, lack of clinical response/treatment failure, participant withdrawal, new requirement for a prohibited concomitant medication, or Investigator judgement. This includes permanent changes of trial treatment to a different TB treatment regimen. It does not include temporary interruptions permitted by the protocol.
- Extension of TB treatment by the Investigator more than 5 days beyond the end of the assigned treatment duration for any reason
- Re-start of TB treatment by the Investigator during the post-treatment follow-up period excluding documented TB re-infection with a different Mtb strain than baseline.
- Positive culture for Mtb at last visit, excluding documented TB re-infection with a different Mtb strain than baseline.

Stage 1 unfavorable outcome status at cross-sectional time points and at the end of treatment (4 months for DBOS and PBOS arms, 6 months for 2HRZE/4HR arm) will inform the decision to proceed to Stage 2. It should be noted that the unfavorable event criteria of TB treatment restart in the post-treatment follow-up period and positive Mtb culture at last visit in post-treatment follow-up period will not be applicable for the Stage 1 primary efficacy endpoint, which focuses on unfavorable outcome status through end of treatment for each arm endpoint.

Unfavorable outcome status will be assessed at 12 months post randomization for the primary efficacy endpoint in Stage 2 and as a secondary endpoint for Stage 1. See Section 1.4 and Section 11.3 for details.

11.4. Statistical Methods

Stage 1 (Phase 2b)

All Stage 1 analyses will be descriptive; no formal hypothesis testing will be performed. For each treatment group (DBOS, PBOS, and 2HRZE/4HR), the proportion of participants with unfavorable status will be summarized at Week 17 for DBOS and PBOS and Week 26 for 2HRZE/4HR. In addition, unfavorable status will be derived for each participant based on truncated data at earlier milestone time points (e.g., at 2, 2.5, 3, 3.5, 4 months) to create snapshots of unfavorable outcome rates across time for each treatment group. Because unfavorable status has a composite definition, summaries will also show which individual components of the composite outcome were met. The Stage 1 efficacy and safety results will be reviewed comprehensively to inform treatment shortening potential and benefit/risk.

Stage 2 (Phase 2c)

In Stage 2, the generalized MCP-Mod methodology (Pinheiro et al, 2014) will be used to implement a duration response modelling strategy to estimate the duration of XBOS that has a rate of unfavorable outcome at 12 months post-randomization that is non-inferior (NI) to 2HRZE/4HR, using a NI margin of 12 percentage points. The first step of the procedure (MCP-step) is used to assess the presence of a duration response signal, using a trend test deducted from a set of

prespecified candidate models. The second step (Mod-step) relies on parametric modelling to find the "optimal" duration for confirmatory study. In a dose response study, which can be extended to a duration response study, the MCP-Mod method is found more effective than pairwise comparison due to its ability to utilize all available data from the continuum of active doses (durations) to estimate a parametric dose-response curve which allows for interpolation and extrapolation of effects across a range of doses (durations).

In the MCP-step, four pre-specified candidate models for the duration response shape of XBOS will be considered in the generalized MCP-Mod method: linear, quadratic, exponential and Emax. First, a logistic regression model will be used with duration as a class variable to get estimates and variances on the logit-transformed proportion of unfavorable outcomes at 12 months post-randomization across the range of durations being tested. These estimates will then be used as inputs into the generalized MCP-Mod procedure to assess the presence of a duration response signal for each of the pre-specified candidate models. A weighted average of the models (weighted by a measure of model quality that penalizes for model complexity) will be used to estimate the duration response shape of the XBOS unfavorable outcome rate at 12 months post-randomization for treatment durations ranging between 9 and 17 weeks. Based on the model fits and variance (estimated using the delta method to back-transform from the logit scale to the probability scale), the minimum treatment duration that is non-inferior to 2HRZE/4HR will be estimated using a non-inferiority margin of 12 percentage points.

Data from both Stage 1 and Stage 2 may be used together in the duration response modelling assessment. Statistical methods to assess "poolability" of the data (eg, Bayesian borrowing techniques) and/or account for potential bias in the data (eg, estimation conditional on progressing to Stage 2) may be utilized.

11.5. Safety

11.5.1. Treatment-emergent AEs, SAEs, and AESI

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), and TEAEs, SAEs and AESIs will be summarized by System Organ Class (SOC), Preferred Term (PT), select Standardized MedDRA Queries (SMQs), and treatment group. TEAEs leading to withdrawal from the trial will also be summarized.

The following will be summarized by treatment group during the treatment period.

- Day of onset of TEAEs
- Duration of TEAEs
- Number of TEAEs reported per participant
- Number and percentage of participants who experience one or more TEAE, one or more SAE, and one or more AESI

The severity grading of each AE, and relationship between the AE and each drug in the regimen, will also be summarized. For participants with more than 1 episode of the same event, the maximum severity grade and maximum relationship to each study drug will be tabulated. Participants reporting more than one occurrence for the PT or SOC being summarized will be counted only once for that PT or SOC.

11.5.2. Safety Laboratory Assessments

All laboratory values collected at visits will be included in the summaries and listings.

Descriptive summaries (n, mean, standard deviation, median, minimum, and maximum) of observed values and change from baseline (last result available on or before receiving the trial intervention) at each scheduled post baseline visit will be presented for each continuous variable test parameter.

Summaries by DAIDS toxicity grade (see Section 13.4, Appendix 4) (and/or the laboratory normal range) and graded shifts in laboratory values from baseline to each post baseline visits will be also presented. All safety laboratory summaries will be presented by treatment group.

11.5.3. ECG Assessments

Descriptive summaries (n, mean, standard deviation, median, minimum, and maximum) of observed values and change from baseline (last result available on or before receiving the trial intervention) at each scheduled post baseline visit will be presented for the following ECG parameters: heart rate, PR interval, QRS duration, QT interval, and QTcF by treatment group.

11.5.4. Other Safety Measures

For vital signs (temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate), summary statistics will be tabulated by treatment group. Frequencies of abnormal vital signs post-dosing will be listed by severity grade. Any other relevant information will be presented in participant data listings. Further details will be provided in the statistical analysis plan (SAP).

11.5.5. Demographic and Compliance Analyses

Demographic parameters (age, sex, and race/ethnicity) and baseline disease characteristics will be summarized descriptively by treatment group for all participants in the safety population.

Listings of randomized participants with protocol deviations (to be defined in the SAP) will be presented by treatment group.

11.6. Interim Analyses

An interim analysis will be performed after all Stage 1 participants finish the end of treatment (17 weeks for DBOS and PBOS and 26 weeks for 2HRZE/4HR) to assess the treatment shortening potential of DBOS and PBOS down to at most 4 months' duration. If neither DBOS nor PBOS shows evidence of treatment shortening potential with an acceptable safety profile, the trial will stop and neither regimen will advance to Stage 2. If only one of the DBOS or PBOS regimens shows evidence of treatment shortening potential with an acceptable safety profile, that regimen

will be considered for progression to Stage 2. If both DBOS and PBOS show evidence of treatment shortening potential with acceptable safety profiles, the regimen that will be considered for proceeding to Stage 2 will be the regimen with the more favorable profile overall as adjudicated by collective deliberation of the partner organizations supporting the conduct of the trial, including, but not limited to, assessment of safety (comparison of rates of SAEs and severe AEs, etc.), tolerability, pharmacokinetics, and alignment with the target regimen profile as outlined in Section 2.1.

Regular monitoring for futility by the IDMC based on the 12-months post-randomization unfavorable outcome rate endpoint will be implemented in both Stage 1 and Stage 2, after at least 20 participants have been enrolled in each group. For each regimen group (PBOS and DBOS administered for 4-months duration in Stage 1) and duration group (XBOS administered for 2, 2.5, 3, 3.5, and 4 months in Stage 2), futility will be declared if the difference in the 12-months post-randomization failure rate of that group minus 2HRZE/4HR exceeds a pre-specified threshold. In Stage 2, because safety events leading to treatment discontinuation are expected to affect efficacy outcomes, a futility decision for a given XBOS arm will not automatically imply futility of XBOS arms of shorter duration; futility will be assessed independently across regimens. For this trial, the pre-specified threshold for futility will be 15 percentage points. The outcome of futility analyses will be non-binding in both stages of the trial.

11.7. Sample Size Justification

Number of Participants

Stage 1 (N=129)
In Stage 1, approximately 43 participants per arm will be enrolled in a 1:1:1 randomization ratio to the treatment groups described in Figure 1.

A subgroup of HIV-infected participants (up to 20%) of the same age range will be enrolled; it is expected that most of these participants will be in South Africa because HIV co-infection is highly prevalent in South Africa but not in other countries planned for trial participation. The trial will be stratified by the following two factors:

- Country/HIV status (Peru, Philippines, South Africa and HIV positive, South Africa and HIV negative); and
- TB disease severity measured by extent of disease on screening chest X-ray (CXR) and mycobacterial burden on screening sputum smear and Xpert Ultra, categorized as follows:
    - High severity: >2 lung zones involved on screening CXR or either screening sputum smear of 3+ or screening sputum Xpert Ultra cycle threshold <18
    - Low/medium severity: ≤2 lung zones involved on screening CXR and screening sputum smear of ≤2+ and screening sputum Xpert Ultra cycle threshold ≥18.

HIV-positive participants must have a CD4+ T-cell count ≥200 cells/μL with HIV RNA copies/mL <200 and cannot have any AIDS-defining opportunistic infections (other than pulmonary TB) or malignancies.

Stage 2 (N=385)
In Stage 2, DS-TB eligible participants will be randomized on Day 1 in a ratio of 2:2:2:2:1:1 to one of the following treatment arms:

- Arm 1 (N=70): XBOS for 2 months (9 weeks)
- Arm 2 (N=70): XBOS for 2.5 months (11 weeks)
- Arm 3 (N=70): XBOS for 3 months (13 weeks)
- Arm 4 (N=70): XBOS for 3.5 months (15 weeks)
- Arm 5 (N=35): XBOS for 4 months (17 weeks)
- Arm 6 (N=35): 2HRZE/4HR regimen for 6 months (26 weeks)

As with Stage 1, a subgroup of HIV-infected participants (up to 20%) of the same age range will be enrolled in Stage 2. The trial will be stratified by country/HIV status and TB disease severity categorized by extent of disease on screening chest X-ray and mycobacterial burden on screening sputum smear and Xpert Ultra (high, low/medium). HIV-positive participants must have a CD4+ T-cell count ≥200 cells/μL with HIV RNA copies/mL <200 and cannot have any AIDS-defining opportunistic infections (other than pulmonary TB) or malignancies.

In Stage 2, RR/MDR-TB eligible participants will also be enrolled into a cohort:

- XBOS in RR/MDR-TB participants (N=35) for 4 months (17 weeks)

Stage 1 (Phase 2b) Simulations

The operating characteristics of the Stage 1 primary endpoint (unfavorable outcome rate at end of treatment) were examined via simulation under binomial distributions with n=43 per treatment group and true unfavorable outcome probabilities as shown in the first and second columns of Table 13. The third column shows, under assumed exponential distributions, the calculated week at which the XBOS unfavorable outcome probability is equal to that of 2HRZE/4HR. For example, if the true unfavorable outcome probability is 0.1 for 2HRZE/4HR at 26 weeks and 0.05 at 17 weeks for XBOS, then XBOS has an unfavorable outcome probability of 0.1 at 13.1 weeks.

Based on simulated data, the final column of Table 13 shows the estimated probability of observing an XBOS unfavorable outcome rate at 17 weeks that is no greater than that of 2HRZE/4HR at 26 weeks. Specifically, with 43 participants per arm, the estimated probability of observing same or improved unfavorable outcome rate with 17 weeks of XBOS relative to 26 weeks of 2HRZE/4HR is 56-58% when the underlying probabilities are equal; 75-87% when the unfavorable outcome probability for XBOS is 5 percentage points lower than 2HRZE/4HR; and above 89% when the unfavorable outcome probability for XBOS is 10 percentage points lower than 2HRZE/4HR.

It is expected that <10% of participants could have pre-treatment baseline sputum culture results negative for growth of drug-susceptible (defined as susceptible to both isoniazid and rifampicin) Mtb. Accounting for exclusion of these participants from the mITT population, the operating characteristics with n=40 per treatment group are similar to those summarized above.

Table 13 Operating Characteristics of Unfavorable Outcome at End of Treatment

Unfavorable outcome probability with n=43 per treatment group			
True 2HRZE/4HR at 26 weeks	**True XBOS at 17 weeks**	**Calculated week when XBOS = 26-week 2HRZE/4HR [a]**	**Estimated probability that XBOS at 17 weeks ≤ 2HRZE/4HR at 26 weeks[b]**
0.10	0.10	17.0	0.58
	0.05	13.1	0.87
0.15	0.15	17.0	0.57
	0.10	14.0	0.81
	0.05	10.8	0.97
0.20	0.20	17.0	0.56
	0.15	14.8	0.75
	0.10	12.7	0.89

a. Based on exponential distribution
b. Proportion of 5000 binomial paired simulations for which the number of XBOS participants with unfavorable outcome is <= the number of 2HRZE/4HR participants with unfavorable outcome (PASS 2022)

Stage 2 (Phase 2c) Simulations

The power to detect a duration response and the operating characteristics around estimating the minimum duration to achieve non-inferiority, based on the upper bound of a 2-sided 95% CI for the difference (XBOS – 2HRZE/4HR) in unfavorable response rates being ≤12% points, was examined under various underlying true duration response profiles and sample size scenarios via clinical trial simulation. The various true duration response profiles examined are shown in Figure 5 and the various sample size scenarios examined are shown in Table 14.

A non-inferiority margin of 12% was selected based on its previous use in a TB treatment shortening trial exploring novel regimens and the Phase 2b/c nature of this trial (Tweed et al, 2021).

Figure 5 Duration Response Profiles Simulated for Stage 2

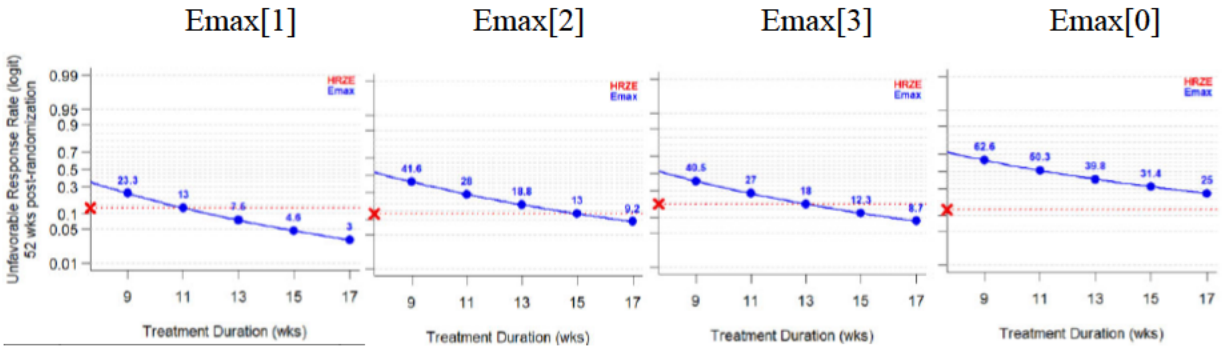


Table 14 Sample Size Scenarios Simulated for Stage 2

	Per Group Sample Size						
Scenario	2HRZE/4HR	9 Weeks XBOS	11 Weeks XBOS	13 Weeks XBOS	15 Weeks XBOS	17 Weeks XBOS	Total N
1	70	70	70	70	70	70	420
2	60	60	60	60	60	60	360
3	50	50	50	50	50	50	300
4	50	50	25	50	25	50	250
5	60	60	30	60	30	60	300
6	60	60	20	60	20	60	280
7	60	60	0	60	30	60	270
8	60	60	0	60	60	30	270

Results are provided in Table 15. With N=70 per group there is greater than 90% power to detect a duration-response effect in all scenarios and the Type I error ($E_{max}[0]$) is <4%. Further, the estimated minimum duration to achieve non-inferiority based on a 95% CI upper bound ≤12% points is generally unbiased.

Table 15 Results of Clinical Trial Simulations for Phase 2

	Emax[1]		Emax[2]		Emax[3]		Emax[0]	
Scenario	Power	Duration Where 95% UB XBOS – 2HRZE/4HR ≤12*	Power	Duration Where 95% UB XBOS – 2HRZE/4HR ≤12*	Power	Duration Where 95% UB XBOS – 2HRZE/4HR ≤12*	Power	Duration Where 95% UB XBOS – 2HRZE/4HR ≤12*
1	97.4	10.6 (9.1, 12.5)	94.1	14.2 (12.2, N/A)	99.2	12.8 (11.0, 14.9)	3.5	N/A (N/A, N/A)
2	94.2	10.8 (9.2, N/A)	88.6	14.4 (12.2, N/A)	97.7	13.0 (10.9, 15.6)	2.9	N/A (N/A, N/A)
3	87.4	11.3 (9.5, N/A)	82.2	14.8 (12.3, N/A)	93.4	13.4 (11.0, N/A)	2.9	N/A (N/A, N/A)
4	78.9	11.7 (9.8, N/A)	78.1	14.9 (12.4, N/A)	90.8	13.6 (11.1, N/A)	2.9	N/A (N/A, N/A)
5	89.6	11.2 (9.4, N/A)	86.4	14.6 (12.2, N/A)	96.4	13.2 (11.0, 16.3)	2.4	N/A (N/A, N/A)
6	87.0	11.3 (9.4, N/A)	83.9	14.7 (12.3, N/A)	94.8	13.4 (11.1, N/A)	2.8	N/A (N/A, N/A)
7	89.0	11.6 (9.6, N/A)	85.8	14.6 (12.3, N/A)	95.6	13.3 (11.2, 16.7)	3.4	N/A (N/A, N/A)

Scenario	Emax[1]		Emax[2]		Emax[3]		Emax[0]	
	Power	Duration Where 95% UB XBOS – 2HRZE/4HR ≤12*	Power	Duration Where 95% UB XBOS – 2HRZE/4HR ≤12*	Power	Duration Where 95% UB XBOS – 2HRZE/4HR ≤12*	Power	Duration Where 95% UB XBOS – 2HRZE/4HR ≤12*
8	87.6	11.6 (9.8, N/A)	77.6	14.5 (12.2, N/A)	92.0	13.2 (11.3, N/A)	3.2	N/A (N/A, N/A)

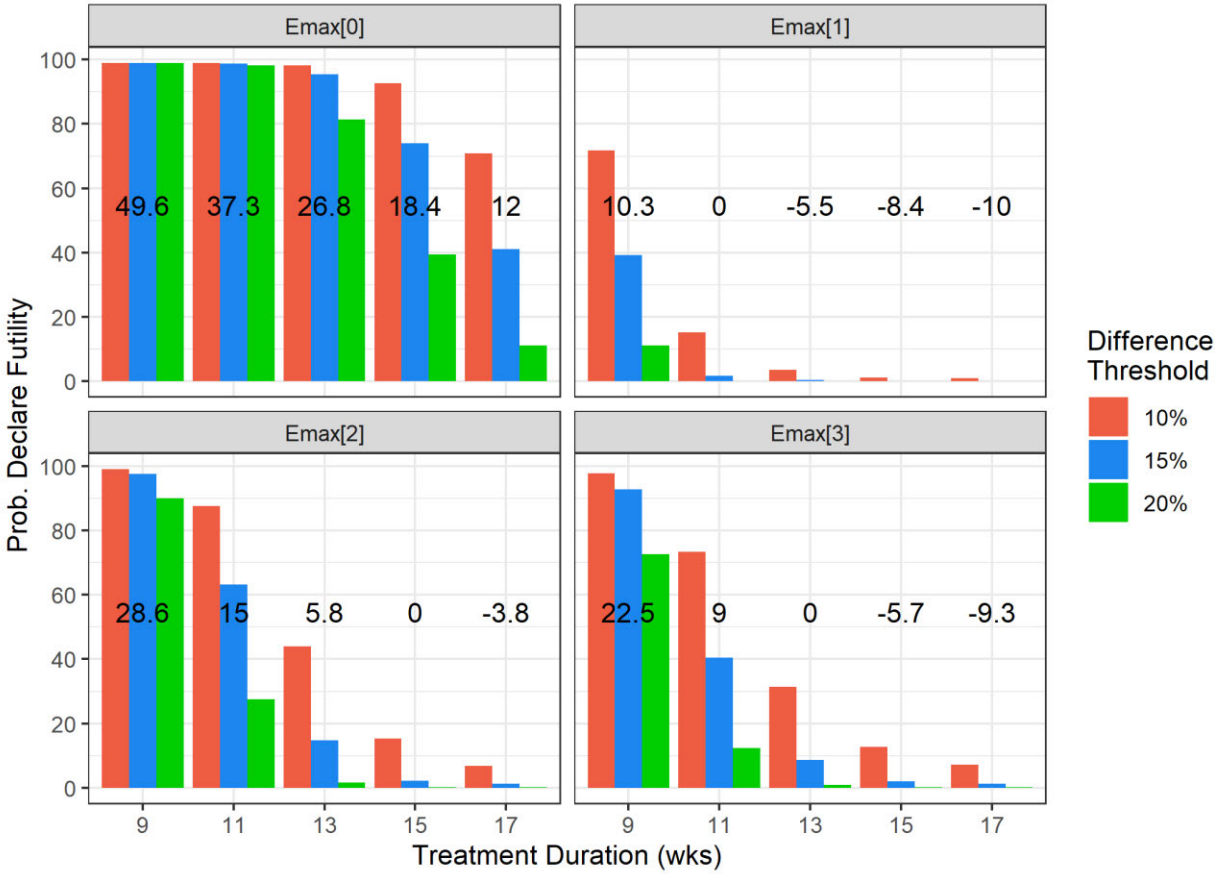
Based on 2000 simulations per row
Power MCP-Mod = Probability that p-value for dose response ≤0.025 and the longest treatment duration that achieves an upper bound for its 2-sided 95% CI in unfavorable response rate (XBOS – 2HRZE/4HR) ≤12% points is 17 weeks duration or less.
* Median (90% lower, upper bound) estimated duration that achieves non-inferiority.
N/A indicates that the median (or 90% lower or upper bound) cannot be estimated without extrapolating beyond 17 weeks treatment duration.

Continuous monitoring for futility

Operating characteristics of a continuous assessment of futility after 20 participants have been enrolled in each duration group were examined via clinical trial simulation using the scenarios described above. Assumptions included 66 weeks of accrual, a constant hazard (ie, probability) of failure over the treatment period and a Weibull hazard (ie, probability) of failure during follow-up where failure is higher early after treatment discontinuation and decreases over time.

Futility will be declared if the difference in the probability of failure (XBOS minus 2HRZE/4HR) exceeds a pre-specified threshold. The probability of declaring futility across varying thresholds is provided in Figure 6. The figure shows that using a threshold of 15% points has very low probability of declaring futility when failure rate favors XBOS and relatively high probability of declaring futility when the failure rate favors 2HRZE/4HR by ≥12% points (null hypothesis). The outcome of futility analyses will be non-binding in both stages of the trial.

Figure 6 Assessing Varying Thresholds of Futility



The differences from HRZE in unfavorable response rate at 52 weeks post-randomization that were simulated in each duration response profile are superimposed on the bar charts. For example, in Emax[0] the unfavorable response rate in the 17 week arm was simulated to be 12 percentage points greater than HRZE's unfavorable response rate.

12. TRIAL COMMITTEES

12.1. Independent Data Monitoring Committee (IDMC)

See Section 1.5 for description of the IDMC that will be established to oversee the safety of this trial.

12.2. Stop Treatment and Watch (STrAW) Concilium

See Section 1.6 for description of the STrAW Concilium.

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1. Appendix 1: List of Prohibited Medications

Potent CYP3A4 Inhibitors:	
Ketoconazole	Voriconazole
Itraconazole	Posaconazole
Lopinavir	Saquinavir
Ritonavir	Tipranavir
Elvitegravir	Indinavir
Cobicistat	Nelfinavir
Clarithromycin	Danoprevir
Telithromycin	Telaprevir
Troleandomycin	Boceprevir
Nefazodone	Conivaptan
Grapefruit juice	Mibefradil
Viekira PAK2	Idelalisib
Moderate CYP3A4 Inhibitors:	
Erythromycin	Faldaprevir
Ciprofloxacin	Amprenavir
Fluconazole	Crizotinib
Diltiazem	Imatinib
Atazanavir	Aprepitant
Verapamil	Casopitant
Atazanavir	Netupitant
Darunavir	Nilotinib
Isavuconazole	Tofisopam
Cimetidine	Dronedarone
Cyclosporine	
Potent CYP3A4 Inducers:	
Carbamazepine	Enzalutamide
Phenytoin	Mitotane
St. John's wort	
Moderate CYP3A4 Inducers:	
Efavirenz	Bosentan
Etravirine	Modafinil
Important CYP3A4 Substrates:	
Nevirapine	Rilpivirine
Etravirine	
BCRP Substrates:	
Sulfasalazine	Methotrexate
Serotonergic Drugs:	
Monoamine oxidase (MAO) inhibitors	
Isocarboxazid	Phenelzine

Tranylcypromine	Selegiline
Moclobemide	
Selective serotonin reuptake inhibitors (SSRIs)	
Citalopram	Escitalopram
Fluoxetine	Fluvoxamine
Paroxetine	Sertraline
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	
Venlafaxine	Desvenlafaxine
Duloxetine	Milnacipran
Levomilnacipran	
Tricyclic antidepressants (TCAs)	
Amitriptyline	Clomipramine
Desipramine	Doxepin
Imipramine	Maprotiline
Nortriptyline	Protriptyline
Trimipramine	Amoxapine
Triptans	
Sumatriptan	Zolmitriptan
Almotriptan	Rizatriptan
Frovatriptan	Naratriptan
Eletriptan	

13.2. Appendix 2. Regulatory, Ethical, and Trial Oversight Considerations

13.2.1. Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, and other relevant documents must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol, ICF, and other relevant documents will require IRB/IEC review and approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants. Amendments to the protocol, ICF, and other relevant documents will also be submitted for review and approval to other bodies, such as local regulatory authorities, in accordance with applicable national and local laws and regulations before implementation.

13.2.2. Trial Oversight

The trial Sponsor, the IRB/IEC, the institution through which the research is performed, and all members of the Investigators' clinical teams and the national regulatory authority share responsibility for ensuring the safety of participants in this trial.

The Investigators will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently, in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH and GCP guidelines, the IRB/IEC, and all other applicable country and local regulatory bodies.
- Closely monitoring trial participants and taking measures necessary to ensure their safety. The Investigator may delay an individual's study drug administration or pause study drug administration altogether if the Investigator is concerned that the study drug might place a participant or participants at significant risk. Where specified, the responsibilities of the Investigator may be delegated to a medically qualified team member (designee). The Investigator determines severity and causality with respect to the study drug for each AE/SAE/AESI.

The Sponsor has an institutional responsibility to ensure participant safety and is ultimately accountable for safety oversight. Local medical monitors and the IDMC play an important role in this regard and support the Sponsor. See Section 1.5 for additional details on the IDMC.

The local medical monitor is the Sponsor's representative and is a physician or surgeon in their country of residence. The local medical monitor:

- reviews the safety of the product for protocols in a specific region and, in conjunction with the Sponsor, determines expectedness of AEs/SAEs/AESIs.
- Is responsible for safety oversight in-country and plays an important role in the reporting of SAEs, AESIs, ADRs, and pregnancies, as described in the protocol.
- In consultation with the Sponsor, may assess the severity and causality for AEs and may upgrade the degree of severity and causality determined by the Investigator.

The IRB or EC has institutional responsibility for the safety of research participants. The IRB or EC has the authority to terminate, suspend, or require changes to the trial.

The national health regulatory authorities have the authority to terminate, suspend, or require changes to the trial.

13.2.3. COVID-19

This protocol includes procedures to minimize the risk of transmission of SARS-CoV-2 among participants and staff in light of the global COVID-19 pandemic and builds on strong infection control site practices, which are already in place at the trial sites, to reduce risk of TB transmission as an airborne infectious disease. Trial sites should follow national and local guidance regarding COVID-19 restrictions and infection prevention and control practices within healthcare facilities and research studies. When adhering to the trial protocol's schedule, assessments, or procedures would result in a participant or trial site being non-compliant with national or local COVID-19 guidelines, the Investigator and/or site should notify the Sponsor immediately.

13.2.4. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

13.2.5. Informed Consent Process

Written informed consent will be obtained prior to conducting any trial-related procedures. Verbal informed consent will be obtained from illiterate and blind participants and an impartial third-party witness will sign the informed consent to document that the participant has gone through the informed consent process and provided their consent. An impartial witness is defined as a person who is independent of the trial, cannot be unfairly influenced by trial team members, attends the informed consent process if the participant cannot read, and who reads the informed consent form

and any other written information supplied to the participant. National and local regulations regarding the informed consent process will be followed.

Participants must be informed that their participation is voluntary. The Investigator or designee will explain the trial to the participant and answer all questions regarding the trial. The Investigator or designee will conduct the consent discussions on an individual basis with each participant. Adequate time will be allowed for all questions to be addressed. Potential participants will be interviewed to ensure that they meet all entry criteria relating to history.

13.2.6. Informed Consent Forms

13.2.6.1. Informed Consent for Trial Participation

Participants will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial center. The informed consent will be obtained by the use of a written consent form approved by the IRB or IEC.

Participants will be asked to provide specific consent for the following assessments/procedures:

- Storage of blood, sputum, and urine samples taken for [redacted] to be used for research not described in this protocol
- Collection of blood for pharmacogenomic testing
- [redacted] (Stage 2 only, Section 9.4.4)

If participants do not provide specific consent for any of these assessments/procedures, they will remain eligible for the trial. Sample testing and processing will be in line with the consent of the participant.

Potential participants with unknown or reported negative HIV status will be tested for HIV due to trial exclusion criteria pertaining to the antiretroviral status, CD4 count, and HIV viral load of HIV-infected individuals (see Section 6.2, criteria 9 and Section 9.2.3). Specific consent for HIV testing will be requested within the main trial consent from potential participants with unknown HIV status, and participants who do not consent to it will not be eligible for the trial.

A copy of the signed consent forms will be given to the participant prior to conducting any trial-related procedures.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If there is a change to the ICF during the conduct of the trial, actively enrolled participants must be re-consented to the most current version of the ICF.

Any withdrawal of consent for sample testing will be documented in the CRF.

Participants will be informed that laboratory tests, [redacted], and subsequent analyses may be conducted in laboratory(ies) working on behalf of the Sponsor (Gates MRI) and located in, but not limited to, South Africa, the Philippines, Peru, Vietnam, Kenya, Uganda, Taiwan, India, United Kingdom, the United States, Australia, and Canada.

Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. Samples will be kept for a maximum of 10 years from the end of the trial.

13.2.7. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant record or dataset that is transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.

The participant must be informed that their trial-related data will be used by the Sponsor in accordance with local data protection law. The level of data disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

13.2.8. Dissemination of Clinical Trial Data

Trial information from this protocol will be posted on publicly available clinical trial registers, such as www.clinicaltrials.gov and clinical trial registries in countries with trial sites, before enrolment of participants begins.

The final study report will include all available safety data, clinical assessments, and concomitant medications through the final trial visit. The database will be locked prior to unmasking and preparation of the final study report. All of the above data must have been entered, reviewed, and all queries related to the data addressed. Modifications or additions to the analyses will be included in the relevant SAP. Any decisions to deviate from the planned analyses described in the protocol and in the SAP will be described in detail in the final study report.

The final clinical study report will be reviewed and approved by the Sponsor signatory and the Investigator.

Summaries of the results of the trial will also be posted on the same websites.

13.2.9. Data Quality Assurance

All participant data relating to the trial will be recorded on printed or electronic CRF using an EDC system, unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. The Investigator must maintain accurate documentation that supports the information entered in the CRF.

The trial will be monitored regularly by the Sponsor or its designee throughout the trial period. The Investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Trial monitors will perform ongoing source data verification to confirm that data entered in the CRFs by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator for 15 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

13.2.10. Source Documents

Source documentation consists of existing medical records and/or trial records developed and maintained by the Investigator. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Data recorded on source documents will be entered onto the CRFs using an EDC system.

Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records.

For the purpose of monitoring and auditing the trial, source documentation will consist of existing medical records, laboratory records, and/or trial records developed and maintained by the Investigator.

13.2.11. Publication Policy

The results of this trial may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13.3. Appendix 3. Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Female/Woman of Childbearing Potential (FOCBP/WOCBP)

A female is considered fertile following menarche. If fertility is uncertain (eg, primary amenorrhea) and a menstrual cycle cannot be confirmed before first dose of trial intervention, additional evaluation should be considered. If in doubt, the participant should be considered fertile.

Females of non-childbearing potential are defined as:

1. Females who are of post-menopausal status. Post-menopausal status is defined as 12 months with no menses without alternative medical cause.
2. Females who have had surgical sterilization (eg, medically documented or participant history of hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation).
3. For females with permanent infertility due to an alternate medical cause other than the above (eg, ovarian failure, Mullerian agenesis, androgen insensitivity). Investigator discretion should be applied to determining trial entry.

Contraception Guidance:

Females of childbearing potential must have a negative serum pregnancy test (β-hCG) at screening prior to randomization. In addition, they must agree to avoid becoming pregnant by using two forms of an acceptable contraceptive method with their male sexual partners or remaining abstinent throughout their participation in the trial. One form of contraception must come from List A and one form from List B. Male and female condoms cannot be used together.

List A	List B
• Hormonal contraception, including pills*, injectables, implants, vaginal rings, and skin patches	• Male or female condom with or without spermicide
• Correctly placed intrauterine device (IUD) or intrauterine system	• Cap, diaphragm, or sponge with spermicide
• Male partner who has had a vasectomy	
* Oral hormonal contraceptives are not an acceptable contraceptive method for female participants of childbearing potential randomized to 2HRZE/4HR due to rifampicin's CYP3A4 induction effect leading to significantly lower levels of oral contraceptives	

Male participants who have not had a vasectomy must agree to use a male or female condom with their female partners of childbearing potential or remain abstinent throughout their participation in the trial to avoid their partners becoming pregnant.

For purposes of the trial, sexual abstinence is defined as not engaging in vaginal sexual intercourse.

Collection and Reporting Pregnancy Information

Female and male participants will be provided with information on acceptable methods of contraception as part of the informed consent process and will be asked to sign the ICF stating that they understand the requirements for avoidance of pregnancy.

The processes outlined below must be followed in the event of a pregnancy occurring in a female trial participant or a female partner of a male trial participant identified during the trial:

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this trial as well as any female partners of male participants that become pregnant. Information will be recorded on the appropriate forms and submitted to the Sponsor within 24 hours of learning of a participant's or participant's partner's pregnancy via email/fax. Female partners of male participants that become pregnant during the trial will be requested to sign a statement of informed consent documenting their willingness to be followed and information about their pregnancy and their child to be collected.
- Investigators must make an effort to collect outcomes of pregnancies discovered during the trial and communicate them to the Sponsor. The health status of the mother and child, the date of delivery, and the child's sex, birth weight and multiparity should be recorded and be reported to the medical monitor after delivery. If delivery occurs before the last scheduled trial visit, the participant should continue to be followed to determine the outcome of the pregnancy and for SAEs through the final trial visit unless withdrawal of consent has occurred. If delivery occurs after the final trial visit, the Investigator should attempt to maintain contact with the participant to obtain information after delivery.
- The Investigator will collect follow-up information on the participant/participant's partner and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 weeks beyond the estimated delivery date unless a longer follow-up period is required by national/local regulations. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be processes as such.
- Any post-trial pregnancy-related SAE considered related to the trial intervention by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former trial participants, he or she may learn of an SAE through spontaneous reporting.

13.4. Appendix 4. Division of Allergy and Infection Diseases (DIAIDs) Adverse Event Reporting

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1
July 2017

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

Table of Contents

Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (*serum glutamic pyruvic transaminase)*
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (*serum glutamic-oxaloacetic transaminase)*
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young Children Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

Instructions for Use

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage
Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies
In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension (with the lowest reading taken after repeat testing during a visit) *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

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Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

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Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

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Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

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Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures *New Onset Seizure* *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

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Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

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Systemic

Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

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*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

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Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ *7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< *7 days of age*	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ *7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< *7 days of age*	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] **or eGFR, Low** **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

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Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

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Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

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Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

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Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

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Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], High (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

13.5. Appendix 5. Document History

DOCUMENT HISTORY	
Document	Date
Original Protocol (Version 1.0):	27 Jun 2022
Amendment 1 (Version 2.0):	13 Oct 2022
Amendment 2 (Version 3.0):	06 Feb 2024

Changes in Version 3.0:

Content-related changes are summarized in the table below. In addition, updates and revisions related to grammar, punctuation, reference format and links, and consistency were also incorporated into this protocol amendment version. The amendment has been classified as an "Other Amendment" according to the Sponsor's relevant standard operating procedure.

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
Sponsor Signatory	Charles D. Wells, MD Head of Therapeutics Development Bill & Melinda Gates Medical Research Institute	David Holtzman, MD, MSc Clinical Development Leader Bill & Melinda Gates Medical Research Insitute
List of Abbreviations		"PTR" added for "Poor Treatment Response"
1.2 Rationale	Bedaquiline is approved by the United States Food and Drug Administration (FDA) as part of combination treatment for adults and children (≥5 years and ≥15 kg) with pulmonary MDR-TB.	Bedaquiline is approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as part of combination treatment for adults and children (≥5 years and ≥15 kg) with pulmonary MDR-TB.
1.2 Rationale	Delamanid is approved by the EMA the European Medicines Agency (EMA) as part of combination treatment for adults and children (≥10 kg) for pulmonary MDR-TB.	Delamanid is approved by the EMA the European Medicines Agency (EMA) as part of combination treatment for adults, children, and infants (≥10 kg) for pulmonary MDR-TB.
1.2 Rationale	Developmental and reproductive toxicology studies in mice, rats, and rabbits have also been completed; the definitive studies support use of sutezolid in clinical studies enrolling women of child-bearing potential (see Section 3.2).	Developmental and reproductive toxicology studies in mice, rats, and rabbits have also been completed; the definitive studies support use of sutezolid in clinical studies enrolling women of child-bearing potential with appropriate measures to prevent pregnancy and informed consent to trial participants, and exclusion criteria for pregnancy and breastfeeding (see Section 3.2).
1.3 Trial Design	These participants with RR/MDR-TB should have documented fluoroquinolone susceptibility to ensure they have at least 1 priority agent from Group A of WHO RR/MDR-TB treatment guidelines to combine with agents from the remaining groups in case additional treatment is required following administration of the experimental regimen (WHO, 2020).	These participants with RR/MDR-TB should have documented fluoroquinolone susceptibility to ensure they have adequate treatment options, including the all oral 9-month regimen or longer individualized regimens as per the recently updated WHO RR/MDR-TB treatment guidelines, in case additional treatment is required following administration of the experimental regimen (WHO, 2022).
1.3.2 Overall Design	• the efficacy and safety of varying durations of administration (in the range of 2 to 4 months) of the combination regimen of DBOS or PBOS in participants with pulmonary DS-TB in comparison with the 2HRZE/4HR regimen as well as sustained sputum culture conversion to negative assessed at the end of 12 months post-randomization (Stage 2)	• the efficacy and safety of varying durations of administration (in the range of 2 to 4 months) of the combination regimen of DBOS or PBOS in participants with pulmonary DS-TB in comparison with the 2HRZE/4HR regimen as assessed by unfavorable outcome status through 12 months of post-randomization follow-up, as well as sustained sputum culture conversion to negative assessed at the end of 12 months post-randomization (Stage 2)
1.3.2 Overall Design	As two of the compounds included in both regimens – OPC-167832 and sutezolid – are investigational and have only been administered for up to 2 weeks in clinical trials in DS-TB patients (Wallis et al, 2014; Dawson et al, 2021),…	As two of the compounds included in both regimens – OPC-167832 and sutezolid – are investigational and have only been administered to a limited number of TB patients in completed and on-going clinical trials in DS-TB patients (Wallis et al, 2014; Dawson et al, 2021; Dawson et al, 2023a; Dawson et al, 2023b; Heinrich et al, 2023; www.clinicaltrials.gov, NCT05221502),…
1.3.5 Number of Participants	In Stage 1, the trial will enroll approximately 129 participants. The screening period will last up to 10 days. A subgroup of HIV-infected participants (up to approximately 20% of total enrollment) will be enrolled; it is expected that most of these participants will be enrolled in South Africa because HIV co-infection is highly prevalent in South Africa but not in other countries planned for Stage 1 trial participation.	In Stage 1, the trial will enroll approximately 129 participants. The screening period will last up to 10 days. HIV-infected participants in Peru will not be eligible for the trial due to the requirement for longer TB treatment courses than the standard 6-month HRZE regimen for patients with HIV/TB co-infection as per the Peruvian national TB treatment guidelines (see Section 6.2). The proportion of HIV-infected participants is not expected to exceed 20% of the total Stage 1 sample size, with most (if not all) to be enrolled in South Africa where HIV co-infection is highly prevalent.

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
1.3.5 Number of Particpants	In Stage 2, the trial will enroll approximately 385 participants. As with Stage 1, a subgroup of HIV-infected participants (up to approximately 20%) will be enrolled.	In Stage 2, the trial will enroll approximately 385 participants. As with Stage 1, a subgroup of HIV-infected participants (up to approximately 20%) will be enrolled. HIV-infected participants in Peru will not be eligible for the trial due to the requirement for longer TB treatment courses than the standard 6-month HRZE regimen for patients with HIV/TB co-infection as per the Peruvian national TB treatment guidelines (see Section 6.2). The proportion of HIV-infected participants is not expected to exceed 20% of the total Stage 2 sample size.
1.3.5 Number of Particpants	Approximately 20% of the participants in the RR/MDR-TB cohort may be HIV-infected.	The proportion of participants in the RR/MDR-TB cohort co-infected with HIV is not expected to exceed 20% of the total RR/MDR-TB cohort size.
1.3.6 Dosing (Stages 1 and 2)	Hospitalization is not required for the trial but may be necessary based on local TB management guidelines.	*Sentence deleted for clarification as no trial sites require hospitalization.*
1.3.6 Dosing (Stages 1 and 2) – Table 1b and Section 7.1.3	A small supply of individual agents comprising the HRZE regimen will also be available for clinical management needs including reintroduction of individual agents with weight-based dosing following treatment interruption.	*Sentence deleted from Table 1b footnote and Section 7.1.3.*
1.3.6 Dosing (Stages 1 and 2) – Table 1b	--	Δ Participant's weight should be rounded down when determining weight band (eg, round 54.9kg to 54kg [Weight Band 2]).
1.3.7 Trial Procedures	Approximately 15 sputum samples per participant will be collected for microbiologic assessment from baseline through…	Sputum samples will be collected for microbiologic assessment at approximately 15 timepoints per participant from baseline through…
1.4 Objectives, Estimands, and Endpoints – Stage 1 and Stage 2 Tables	• Objective o To evaluate emergence of anti TB drug resistance • Estimand o In participants receiving at least 1 dose of trial intervention, the proportion of participants that develop resistance against each drug at any point during the 12 months post randomization by treatment group • Endpoints o Resistance to delamanid or pretomanid, bedaquiline, OPC-167832, and/or sutezolid, or to isoniazid, rifampicin, pyrazinamide, and/or ethambutol through 12 months post randomization	• Objective o To evaluate emergence of anti TB drug resistance • Estimand o In participants receiving at least 1 dose of trial intervention, the proportion of participants that develop resistance against ≥1 drug during the 12 months post randomization by treatment group (Note: resistance determination will only be reported for bedaquiline and delamanid among DBOS and PBOS agents as they are the only agents with accepted WHO-recommended critical concentrations). o In participants receiving at least 1 dose of trial intervention, the change in minimum inhibitory concentration (MIC) from baseline to post-baseline for delamanid, pretomanid, bedaquiline, OPC-167832, and sutezolid during the 12 months post randomization by treatment group. • Endpoints (Stage 1) o Resistance result among baseline sputum culture and first culture positive for Mtb at Week 13 or afterwards through 12 months post randomization for delamanid, bedaquiline, isoniazid, rifampicin, pyrazinamide, and/or ethambutol through 12 months post randomization.

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
		○ MIC values of delamanid, pretomanid, bedaquiline, OPC-167832, and sutezolid performed on baseline sputum culture and first culture positive for Mtb at Week 13 or afterwards through 12 months post randomization. • Endpoints (Stage 2) ○ Resistance result among baseline sputum culture and first culture positive for Mtb at Week 9 or afterwards for Arm 1, Week 11 or afterwards for Arm 2, and Week 13 or afterwards for Arms 3 to 6 and the RR/MDR-TB cohort through 12 months post randomization for delamanid, bedaquiline, isoniazid, rifampicin, pyrazinamide, and/or ethambutol ○ MIC values of delamanid, pretomanid, bedaquiline, OPC-167832, and sutezolid performed on baseline sputum culture and first culture positive for Mtb at Week 9 or afterwards for Arm 1, Week 11 or afterwards for Arm 2, and Week 13 or afterwards for Arms 3 to 6 and the RR/MDR-TB cohort through 12 months post randomization.
1.4 Objectives, Estimands, and Endpoints – Stage 2 Table	○ Objective ○ To assess the efficacy of the combination regimen of XBOS in participants with DS-TB and HIV co-infection at the end of treatment ○ Endpoints ○ Unfavorable outcome status amongst participants with DS-TB and HIV co-infection (12 months post randomization)	○ Objective ○ To assess the efficacy of the combination regimen of XBOS in participants with DS-TB and HIV co-infection at the end of treatment and 12 months post-randomization ○ Endpoints ○ Unfavorable outcome status amongst participants with DS-TB and HIV co-infection (end of treatment and 12 months post randomization)
1.4 Objectives, Estimands, and Endpoints – Stage 2 Table	○ Objective ○ To evaluate and compare the change in solid culture outcomes in participants receiving the combination regimen of XBOS relative to 2HRZE/4HR ○ Estimand	○ Objective ○ To evaluate and compare the change in solid culture outcomes in participants receiving the combination regimen of XBOS relative to 2HRZE/4HR ○ Estimand (additional estimand added) ○ Difference in proportion with sustained sputum culture conversion to negative at Week 8 and EOT (pooled XBOS arms minus 2HRZE/4HR).
1.6 Stop Treatment and Watch (STrAW) Concilium	The STrAW Concilium will be established for the trial for the following purposes: • Monitor individual trial participants' response to treatment through the review of standardized data reports produced at important time	The STrAW Concilium will be established for the trial ~~for the following purposes~~: • ~~Monitor individual trial participants' response to treatment through the review of standardized data reports produced at important time points (these reports will not indicate a participant's assigned treatment regimen).~~

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
	points (these reports will not indicate a participant's assigned treatment regimen). • Provide expert clinical consultation to Investigators on challenging clinical scenarios, including all participants where the Investigator wants to permanently stop one or more trial medications, continue trial treatment past the assigned duration, or restart TB treatment after the completion of trial treatment (see Section 8.3.2 and Section 9.5.4).	• To provide expert clinical consultation to Investigators on challenging clinical scenarios, including all participants where the Investigator wants to permanently stop one or more trial medications, continue trial treatment past the assigned duration, or restart TB treatment after the completion of trial treatment (see Section 8.3.2 and Section 9.5.4).
1.7 Schedule of Activities – Table 3 and Table 4	DBOS or PBOS Treatment/XBOS Treatment (Arms 1 and 2 – Table 3; Arms 1-5 – Table 4) 2HRZE/4HR Treatment (Arm 3 – Table 3; Arm 6 – Table 4) XBOS Treatment (RR/MDR-TB Arm – Table 4)	• 'X' added to Visit 2 (Baseline Visit) to coincide with Day 1 (first day of study treatment administration)
1.7 Schedule of Activities – Table 3 and Table 4	Vital signs	• 'X' added to Visit 13 (Week 19) and 15 (Week 23) with following addition to footnote 'j': "Weight should be measured at Week 19 and Week 23 visits for Arm 3/6 participants to inform any weight-based dose adjustment required (no other vital signs are required at Week 19 or Week 23 visits)."
1.7 Schedule of Activities – Table 3 and Table 4	TB Signs & Symptoms Questionnaire	• Removed from Screening Visit • Footnote 'e' reworded to: TB Signs & Symptoms Questionnaire will include a structured questionnaire and cough status assessment.
1.7 Schedule of Activities – Table 3 and Table 4	Visual assessment	• 'X' added to Screening Visit to reflect fundoscopy conducted at that visit.
1.7 Schedule of Activities – Table 3 and Table 4	IMP dispensing and IMP adherence assessment	• 'X' added to Visit 13 (Week 19 – Table 4 only) and Visit 15 (Week 23 – Table 3 and Table 4) with reference added to footnote 'j': "Only Arm 3 (2HRZE/4HR participants) will receive IMP treatment from Weeks 18-26. Weight should be measured at Week 19 and Week 23 visits for Arm 3 participants to inform any weight-based dose adjustment required (no other vital signs are required at Week 19 or Week 23 visits)."
1.7 Schedule of Activities – Table 3 and Table 4	Footnote **: Week number represents the last day of the respective week (eg, Week 1 assessment = Day 7; Week 2 assessment = Day 14, etc.)	Footnote **: Week number represents the last day of the respective week (eg, Week 1 assessment = Day 8; Week 2 assessment = Day 15, etc.)
1.7 Schedule of Activities – Table 3 and Table 4	Footnote 'd': "The following vital signs should be measured at every visit: temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight. Height will be measured only at screening. Oxygen saturation, blood pressure, heart rate, and respiratory rate should be measured in the sitting or supine position after the participant has rested for ≥2 minutes."	Footnote 'd': "The following vital signs should be measured at every visit: temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and weight. Height will be measured only at screening. Body mass index (BMI) will be calculated at every visit that weight is measured using the height measured at the screening visit. Oxygen saturation, blood pressure, heart rate, and respiratory

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
		rate should be measured in the sitting or supine position after the participant has rested for ≥2 minutes. Vital signs do not need to be recorded at Week 19, Week 23, and Week 28 visits except for weight at Week 19 and Week 23 visits for participants in Arm 3/6 (2HRZE/4HR) to inform any weight-based dose adjustment indicated."
1.7 Schedule of Activities – Table 3 and Table 4 and Section 9.5.1.1 (Initial Screening Visit)	Footnote 'n': "HIV rapid testing should be done during screening if: a) the participant's last HIV negative test was >1 month prior to screening or b) the participant reports being HIV infected but cannot provide written documentation of their HIV status at screening, such as documentation in a medical record or book…"	Footnote 'n': "HIV testing should be done during screening if: a) the participant's HIV status is unknown, b) the participant reports being HIV negative or c) the participant reports being HIV infected but cannot provide written documentation of their HIV status at screening, such as documentation in a medical record or book…."
1.7 Schedule of Activities – Table 3 and Table 4	• Footnote 'p' (Table 3): "PK samples will be taken on the following schedule for participants randomized to Arms 1 and 2. PK will not be assessed for Arm 3 (2HRZE/4HR). Baseline visit (to serve as predose sample), Week 1 (predose and 2-6 h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6 h postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), Week 17 (predose), Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12 (18 samples per participant). Random post-treatment PK samples will be collected and tested for bedaquiline and its metabolite only…" • Footnote 'q' (Table 4): "PK samples will be taken on the following schedule for participants randomized to Arms 1 to 5 and RR/MDR-TB cohort. PK will not be assessed for Arm 6 (2HRZE/4HR). Baseline visit (to serve as predose sample), Week 1 (predose and 2-6h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6h postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), Week 17 (predose), Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12. (18 samples per participant). Random post-treatment PK samples will be collected and tested for bedaquiline and its metabolite only…"	• Footnote 'p' (Table 3): "PK samples will be taken on the following schedule for participants randomized to Arms 1 and 2 (PK will not be assessed for Arm 3 [2HRZE/4HR]): Baseline visit (to serve as predose sample), Week 1 (predose and 2-6 h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6 h postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), and Week 17 (predose). PK samples will be collected at the following post-treatment study visits for testing of bedaquiline and its metabolite only: Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12. 18 PK samples will be collected per participant in total…" • Footnote 'q' (Table 4): "PK samples will be taken on the following schedule for participants randomized to Arms 1 to 5 and RR/MDR-TB cohort (PK will not be assessed for Arm 6 [2HRZE/4HR]): Baseline visit (to serve as predose sample), Week 1 (predose and 2-6h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6h postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), and Week 17 (predose). PK samples will be collected at the following post-treatment study visits for testing of bedaquiline and its metabolite only: Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12. 18 PK samples will be collected per participant in total…"
1.7 Schedule of Activities – Table 3 and Table 4	Footnote 'q' (Table 3) and Footnote 'r' (Table 4): "For women of childbearing potential only, serum β-hCG will be collected at the first screening visit. Point-of-care urine pregnancy testing will be done at the baseline visit and approximately every 3-4 weeks throughout the trial."	Footnote 'q' (Table 3) and Footnote 'r' (Table 4): "For women of childbearing potential only, serum β-hCG will be collected at the first screening visit. Point-of-care urine pregnancy testing will be done at the baseline visit. After randomization, either point-of-care urine pregnancy testing or serum β-hCG testing will be performed approximately every 3-4 weeks throughout the trial."
1.7 Schedule of Activities –	Footnote 'r' (Table 3) and Footnote 't' (Table 4): "Pharmacogenomic sample collection will only be performed for participants that provide specific consent for it.	Footnote 'r' (Table 3) and Footnote 't' (Table 4): "Pharmacogenomic sample collection will only be performed for participants that provide specific consent for it.

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
Table 3 and Table 4	Microscopic examination for red blood cells, white blood cells, casts, bacteria, and other abnormalities will be performed if urine dipstick is positive for protein, blood, leukocyte esterase, or nitrites or if otherwise indicated."	~~Microscopic examination for red blood cells, white blood cells, casts, bacteria, and other abnormalities will be performed if urine dipstick is positive for protein, blood, leukocyte esterase, or nitrites or if otherwise indicated~~."
1.7 Schedule of Activities – Table 3 and Table 4	Footnote 'u' (Table 3) and Footnote 'w' (Table 4): "One spot sputum will be collected at the initial screening visit. At baseline visit, three spot sputum specimens will be collected…"	Footnote 'u' (Table 3) and Footnote 'w' (Table 4): "One spot sputum will be collected at the initial screening visit. At baseline visit, three spot sputum specimens will be collected before the first dose of study treatment is administered…"
1.7 Schedule of Activities – Table 3 and Table 4	Footnote 'v' (Table 3) and Footnote 'y' (Table 4): "Sputum pellets and culture isolates will be stored for all positive cultures for DST, genotyping, and any repeat testing that may be required."	Footnote 'v' (Table 3) and Footnote 'y' (Table 4): "Mtb culture isolates will be stored for all positive cultures for DST/MIC, genotyping, and any repeat/exploratory testing that may be required."
1.7 Schedule of Activities – Table 3 and Table 4	• Footnote 'x' (Table 3): "Mtb genotyping will be performed on a baseline culture from baseline visit or Week 1 depending on suitability of culture growth as well as the first of any subsequent positive culture during the post-treatment follow-up period for suspected relapse cases (the post-treatment follow-up period begins after the Week 17 visit for Arms 1 and 2 and after the Week 26 visit for Arm 3)…" • Footnote 'aa' (Table 4): "Mtb genotyping will be performed on a baseline culture from baseline visit or Week 1 depending on suitability of culture growth as well as the first of any subsequent positive culture during the post-treatment follow-up period for suspected relapse cases (post-treatment follow-up period starts at Week 11 visit for Arm 1, Week 13 for Arm 2, Week 15 for Arm 3, Week 17 for Arm 4, Week 19 for Arm 5 and RR/MDR-TB cohort, and Week 28 visit for Arm 6)…"	• Footnote 'x' (Table 3): "Genotyping will be performed on a Mtb-positive culture from baseline visit or Week 1 depending on suitability of culture growth as well as the first of any subsequent Mtb-positive culture occurring from the end of treatment study visit through the end of the post-treatment follow-up period for suspected relapse cases (the post-treatment follow-up period begins at the Week 17 visit for Arms 1 and 2 and at the Week 26 visit for Arm 3). • Footnote 'aa' (Table 4): "Genotyping will be performed on a Mtb-positive culture from baseline visit or Week 1 depending on suitability of culture growth as well as the first of any subsequent Mtb-positive culture occurring from the end of treatment study visit through the end of the post-treatment follow-up period for suspected relapse cases (post-treatment follow-up period starts at the respective end-of-treatment visit for each arm)…"
2 Introduction	"…. It requires treatment with World Health Organization (WHO)-designated Class A drugs (fluoroquinolones, bedaquiline, and linezolid) reserved for use in patients with rifampicin or multi drug resistant disease to serve as the backbone for treatment combined with other reserve agents (delamanid, cycloserine, clofazimine, ethionamide, PAS, etc.) and generally must be administered for a longer duration (9 to 18 months), and often with lower cure rates and added side-effects (WHO, 2020)…"	"…It requires treatment for a minimum of 6 months with the WHO-recommended BPaLM (bedaquiline, pretomanid, linezolid, moxifloxacin) or BPaL (bedaquiline, pretomanid, linezolid) regimens based on fluoroquinolone susceptibility, the all oral bedaquiline or linezolid based 9-month all oral regimen, or a longer 18-month individualized regimen based on a hierarchical grouping of second-line TB medicines, the drug-resistance profile and the patient's medical history; all treatment options require close medical monitoring. (WHO, 2022)…"
2.1 Trial Rationale	"…The active TRUNCATE-TB trial is investigating four 2-month regimens that add or replace 1-2 agents in HRZE (www.clinicaltrials.gov, NCT03474198)…"	"…The TRUNCATE-TB trial which investigated four 2-month regimens that added or replaced 1-2 agents in HRZE (www.clinicaltrials.gov, NCT03474198) demonstrated that the bedaquiline–linezolid containing regimen was noninferior to HRZE with respect to clinical outcomes; the strategy was associated with a shorter total duration of treatment and with no evident safety concerns (Paton et al, 2023)…"
3.1.1.1.3 DS-TB (Bedaquiline)	"…Additionally, an open-label, partially randomized trial to evaluate the efficacy and safety of treatment with bedaquiline in combination with pretomanid, moxifloxacin and pyrazinamide (BPaMZ) administered for 4 months in DS-TB is on-going with trial completion projected for 2022	"…Additionally, an open-label, partially randomized trial to evaluate the efficacy and safety of treatment with bedaquiline in combination with pretomanid, moxifloxacin and pyrazinamide (BPaMZ) administered for 4 months in DS-TB(www.clinicaltrials.gov; NCT03338621) completed in 2022 validated

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	(www.clinicaltrials.gov; NCT03338621). A separate open-label, randomized trial to evaluate the 14-day efficacy and safety of bedaquiline combined with OPC-167832 as well as bedaquiline combined with OPC-167832 and delamanid in DS-TB is currently enrolling (the trial's primary focus is on the early bactericidal activity and safety of OPC 167832) (www.clinicaltrials.gov; NCT03678688)."	observations from pre-clinical relapsing mouse model experiments which identified BPaMZ as a regimen with high efficacy and treatment shortening potential, but hepatic toxicity precluded treatment completion in approximately 6-7% of patients (Eristavi et al, 2023). A complementary multi-study analysis showed that Pa-Z-containing regimens were associated with a hepatic safety profile distinct from BPaL, with a higher incidence and degree of grade 4 alanine transaminase elevations. A separate open-label, randomized trial to evaluate the 14-day efficacy and safety of bedaquiline combined with OPC-167832 as well as bedaquiline combined with OPC-167832 and delamanid in DS-TB demonstrated that the combinations were well tolerated and the three-drug combination exhibited similar early bactericidal activity to HRZE supporting further evaluation for longer term treatment (www.clinicaltrials.gov; NCT03678688; Dawson et al, 2023b)."
3.1.2.1.2 Delamanid Safety	--	"Additionally, several psychiatric adverse drug reactions have been described for delamanid, including psychotic disorder, anxiety, depression, and hallucinations. Cases of hallucination have predominantly been reported in the pediatric population in post-marketing surveillance though were observed in 5.4% of children in delamanid clinical trials and 1% of adults (Deltyba™ SmPC, 2023)."
3.1.2.2 DS-TB (Delamanid)	"An open-label, randomized trial to evaluate the 14-day efficacy and safety of delamanid combined with OPC 167832 as well as delamanid combined with OPC-167832 and bedaquiline in DS-TB is currently enrolling (the trial's primary focus is on the early bactericidal activity and safety of OPC 167832) (www.clinicaltrials.gov; NCT03678688)."	"An open-label, randomized trial to evaluate the 14-day efficacy and safety of delamanid combined with OPC 167832 as well as delamanid combined with OPC-167832 and bedaquiline in DS-TB was completed and the combination exhibited similar early bactericidal activity to HRZE supporting further evaluation for longer term treatment (Dawson et al, 2023b; www.clinicaltrials.gov, NCT05221502)."
3.1.3.2.1 Pretomanid Efficacy	"There is an on-going open-label, partially randomized trial to evaluate the efficacy and safety of treatment with pretomanid (200 mg) in combination with bedaquiline, moxifloxacin and pyrazinamide (BpaMZ) administered for 4 months in DS-TB; trial completion is projected for 2022 (www.clinicaltrials.gov; NCT03338621)."	"The open-label, partially randomized trial to evaluate the efficacy and safety of treatment with pretomanid (200 mg) in combination with bedaquiline, moxifloxacin and pyrazinamide (BPaMZ) administered for 4 months in DS-TB validated observations from pre-clinical relapsing mouse model experiments identifying BPaMZ as a regimen with high efficacy and treatment shortening potential, but hepatic toxicity precluded treatment completion in approximately 6-7% of patients; a complementary multi-study analysis showed that Pa-Z-containing regimens were associated with a hepatic safety profile distinct from BPaL, with a higher incidence and degree of grade 4 ALT elevations.(www.clinicaltrials.gov; NCT03338621; Eristavi et al, 2023)."
3.1.3.2.2.1 Risk of Testicular Toxicity (Pretomanid)	"The effect of pretomanid on sex hormones in male participants was evaluated in 4 pretomanid containing clinical trials, including one of 26 weeks duration. In that study, there were no changes in follicle stimulating hormone, inhibin B, luteinizing hormone, and testosterone that were attributed to treatment with pretomanid. A 6-month study focused on addressing the reproductive safety of pretomanid in male DR-TB patients is ongoing (www.clinicaltrials.gov; NCT04179500).	"The effect of pretomanid on sex hormones in male participants (follicle-stimulating hormone, luteinizing hormone, inhibin B, and testosterone) was evaluated in 4 pretomanid containing clinical trials, including one of 26 weeks duration. Overall, these hormone assessments demonstrated an improvement in the underlying hypogonadism, as reflected by increases in testosterone and inhibin B levels, in all treatment arms, consistent with improvements in the underlying disease state. In addition, no adverse events associated with fertility disorders

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	The potential risk for testicular toxicity will be highlighted during the informed consent process for males being screened for participation in this clinical trial."	among male participants were identified across 19 studies in the pretomanid clinical development program (Pretomanid Investigator's Brochure, 2023). A retrospective survey of male participants that had received pretomanid in 4 studies or HRZE in 2 studies was conducted to evaluate the number of partner births that had occurred while the male participant had received pretomanid or HRZE or afterwards. The adjusted rate ratio of incidences of fathering at least 1 child after the start of study treatment was 0.98 (95% CI 0.47, 2.03, p=0.957) suggesting pretomanid does not have an effect on fertility compared with HRZE (Pretomanid Investigator's Brochure, 2023). A 6-month study focused on addressing the reproductive safety of pretomanid in adult male DR-TB patients receiving the BPaMZ regimen has completed enrollment with results on the primary endpoint of change in sperm count from baseline to week 26 included in the current Investigator's Brochure. The mean total sperm count and sperm concentration increased from baseline throughout treatment to week 26 with no change in semen volume. These results suggest treatment with a pretomanid-containing regimen for up to 6 months does not adversely affect human spermatogenesis. Full trial results are expected in 2024 (Pretomanid Investigator's Brochure, 2023; www.clinicaltrials.gov; NCT04179500). The potential risk for testicular toxicity will be highlighted during the informed consent process for males being screened for participation in this clinical trial."
3.2.1.2 Clinical (OPC-167832)	"Evaluation of combination delamanid, bedaquiline and OPC 167832 administration is currently ongoing (see Section 3.3.1.2 for more details)."	"The combination of delamanid, bedaquiline and OPC 167832 was first evaluated in the second part of the 14-day EBA trial; the combination exhibited similar early bactericidal activity to HRZE supporting further evaluation for longer term treatment (Dawson et al, 2023b). This combination is currently ongoing assessment in a longer-term (4 months) treatment trial with results anticipated by 2025 (www.clinicaltrials.gov, NCT05221502; see Section 3.3.1.2 for more details)."
3.2.2.1.1 Toxicology (Sutezolid)	"…These definitive developmental and reproductive toxicology studies support use of sutezolid in clinical studies enrolling women of child-bearing potential. Addition of sutezolid in a PBOS or DBOS regimen will not have any additional reproductive potential risk."	"…These definitive developmental and reproductive toxicology studies support use of sutezolid in clinical studies enrolling women of child-bearing potential. In a fertility and early embryonic development study, sutezolid had no effect on fertility in either sex or on early embryonic development in females at any dose tested up to safety multiples of ~4-fold in males or females. In the pre- and post-natal development study, there was a dose-dependent increased incidence in pup mortality at safety multiples of ≥ 1-fold to sutezolid in the absence of maternal toxicity. No abnormalities were identified following neurobehavioral assessment or in reproductive performance in surviving pups in the F1 generation at the NOAEL dose of 30 mg/kg/day. Addition of sutezolid in a PBOS or DBOS

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		regimen will not have any additional reproductive potential risk. The new findings of perinatal pup losses with sutezolid should not preclude the inclusion of females of childbearing potential in a clinical trial with an informed consent that includes precautions to guard against pregnancy, and exclusion criteria for pregnancy or breastfeeding."
3.2.2.2 Clinical (Sutezolid)	"Sutezolid has been studied in single and multiple ascending dose (MAD) trial in healthy volunteers and in a 14 day EBA trial in TB patients (Wallis et al, 2010; Wallis et al, 2011; Wallis et al, 2014)… No clinical data exist for durations of administration exceeding 28 days."	"Sutezolid has been studied in a single and multiple ascending dose (MAD) trial in healthy volunteers, in a 14 day EBA trial in TB patients, and in a Phase 2b dose-ranging trial in combination with bedaquiline, delamanid, and moxifloxacin for 4 months (Wallis et al, 2010; Wallis et al, 2011; Wallis et al, 2014; Heinrich et al, 2023)…In an open-label, randomized, controlled trial assessing the safety and efficacy of a range of sutezolid doses (600 mg QD, 600 mg BID, 800 mg BID and 1200 mg QD) administered over 12 weeks to patients with pulmonary DS-TB in combination with bedaquiline, delamanid, and moxifloxacin, the combination was well tolerated with no neuropathy nor myelosuppression identified (except one case of neutropenia with a possible alternative cause). Additionally, there was only one participant with hepatotoxicity requiring treatment interruption observed although treatment was successfully reintroduced.; However, there was no clear dose-effect on slope of MGIT TTP over 12 weeks for sutezolid which may have been due to a limitation in trial design (Heinrich et al, 2023). ~~No clinical data exist for durations of administration exceeding 28 days.~~"
3.2.2.2.1 Potential Oxazolidinone Class Effects	"The safety of protracted dosing with sutezolid, and its safety in combination with other drugs, is not established. Close monitoring of potential safety concerns is indicated."	"~~The safety of protracted dosing with sutezolid, and its safety in combination with other drugs, is not established.~~ Close monitoring of potential safety concerns is indicated in the trial given the limited number of participants exposed to longer dosing with sutezolid in combination with other drugs."
3.2.3 Potential Drug-Drug Interactions…	"…A Phase 2a 14-day evaluation of the EBA of OPC-167832 in combination with bedaquiline and delamanid is ongoing and will provide information on the PK drug-drug interactions potential for those drugs prior to starting this trial…"	"…A Phase 2a 14-day evaluation of the EBA of OPC-167832 in combination with bedaquiline and delamanid completed in 2022 demonstrated no apparent clinically significant PK drug-drug interactions for the combination (OPC-167832 Investigator's Brochure, 2024; Dawson et al, 2023b)…"
3.3.1.2 Supportive Evidence from Combination Evaluation… and 3.3.1.3.3 OPC-167832 Dose Selection and Rationale	"…A follow-on Phase 2b trial sponsored by Otsuka Pharmaceuticals evaluating OPC-167832 administered as 10 mg, 30 mg, or 90 mg daily in combination with bedaquiline and delamanid for 4 months in patients with DS-TB is currently enrolling in South Africa (www.clinicaltrials.gov; NCT05221502)."	"…A follow-on Phase 2b trial sponsored by Otsuka Pharmaceuticals evaluating OPC-167832 administered as 10 mg, 30 mg, or 90 mg daily in combination with bedaquiline and delamanid for 4 months in patients with DS-TB has completed enrollment in South Africa and is still ongoing with results anticipated by 2025 (www.clinicaltrials.gov; NCT05221502)."
3.3.1.3.4 Sutezolid Dose Selection and Rationale	--	"…Though a more recently completed open-label, randomized, controlled trial assessing the safety and efficacy of a range of sutezolid doses (600 mg QD, 600 mg BID, 800 mg BID and 1200 mg QD) administered over 12 weeks to patients with pulmonary DS-TB in combination with bedaquiline, delamanid, and moxifloxacin demonstrated no clear dose-effect on slope of TTP from sputum

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		cultures likely due to trial design limitations, the combination with all doses of sutezolid evaluated was well tolerated including no neuropathy nor myelosuppression identified (except one case of neutropenia with a possible alternative cause) (Heinrich et al, 2023)."
3.3.1.4 Summary for DBOS and 3.3.2.4 Summary for PBOS	"…Although OPC-167832 and sutezolid have only been administered for 2 weeks as monotherapy among DS-TB, the favorable safety profile from their EBA trial coupled with favorable results from toxicology studies for their longer-term use support their evaluation with delamanid and bedaquiline in this trial."	"…Although there is limited data on OPC-167832 and sutezolid when administered for longer than 2 weeks and/or in combination with other anti-TB agents, the favorable safety profile from their trials coupled with favorable results from toxicology studies for their longer-term use support their evaluation with delamanid and bedaquiline in this trial."
3.3.2.4 Summary for PBOS	"…. A 6-month trial focused on addressing the reproductive safety of pretomanid in male DR-TB patients is ongoing (see Section 3.1.3.2.2.1)."	"…Results from a recently completed trial focused on addressing the reproductive safety of pretomanid administered as part of the 6-month BPaMZ regimen to male DR-TB patients demonstrated no adverse effects of the pretomanid-containing regimen on human spermatogenesis as measured by change in mean total sperm count and sperm concentration over 6 months (see Section 3.1.3.2.2.1)."
6.1 Inclusion Criteria	4) Newly diagnosed within the past 3 weeks prior to informed consent…	4) Newly diagnosed within the past 8 weeks prior to informed consent…
6.2 Exclusion Criteria	--	(Addition) 9e) HIV-infected participants enrolling at a trial site in Peru will not be eligible due to the requirement for longer TB treatment courses than the standard 6-month HRZE regimen for patients with HIV/TB co-infection as per the Peruvian national TB treatment guidelines.
8.3.2 Permanent Discontinuation of Trial Treatment	"Investigators should discuss decisions regarding the permanent discontinuation of one or more trial investigational medications for a participant with the STrAW Concilium and inform the Sponsor (see Section 1.6). See Section 9.5.4 for further details of the evaluation and management of participants permanently discontinued from trial treatment."	"Investigators should discuss decisions regarding the permanent discontinuation of one or more trial investigational medications for a participant with the STrAW Concilium and inform the Sponsor (see Section 1.6). TB treatment should not be permanently changed, stopped, or restarted before consultations with the STrAW Concilium have been completed if the participant's clinical condition permits. See Section 9.5.4 for further details of the evaluation and management of participants permanently discontinued from trial treatment."
9.1.3 Review of Systems Including TB Signs and Symptoms	"TB signs and symptoms will be specifically assessed at screening and every scheduled trial visit in addition to the broader review of systems. A structured questionnaire will be utilized that includes the WHO 4-symptom TB screen and questions focused on cough frequency and characteristics, impact of cough on daily activities, and other symptoms of chronic pulmonary conditions…"	"TB signs and symptoms will be assessed by the Investigator at the Screening Visit to assess eligibility (see Section 6.1). From the Baseline Visit (Visit 2) onward, a structured protocol-specific questionnaire (TB Signs and Symptoms Questionnaire) will be utilized that includes the WHO 4-symptom TB screen and questions focused on cough frequency and characteristics, impact of cough on daily activities, and other symptoms of chronic pulmonary conditions…"
9.1.7 Vital Signs	--	"…Body mass index will be calculated at every visit that weight is measured using the height measured at the screening visit…"
9.2.3 HIV Testing	"Rapid HIV testing will be conducted at screening for participants whose last documented negative HIV test was conducted more than 30 days before signing informed consent…"	"HIV testing will be conducted at screening for participants…".
9.2.8 Pregnancy Testing	"…Point-of-care urine β-hCG testing will also be conducted at the baseline visit and approximately every 3 to 4 weeks post-randomization at trial visits for all participants who are FOCBP until 12 weeks after last dose of trial drug."	"…Point-of-care urine β-hCG testing will also be conducted at the baseline visit. After randomization, point-of-care urine or serum β-hCG testing will be conducted

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		approximately every 3 to 4 weeks post-randomization at trial visits for all participants who are FOCBP until 12 weeks after last dose of trial drug."
9.2.10 PK Sampling	• Post-treatment PK samples will be collected and tested for bedaquiline and its metabolite only.	• Post-treatment random PK samples (Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12) will be tested for bedaquiline and its metabolite only.
9.2.10 PK Sampling	"The predose blood draw should be drawn approximately 15 minutes prior to the daily dose of DBOS or PBOS…"	"The predose blood draw should be drawn approximately 15 minutes prior to the daily dose of DBOS or PBOS except for the Day 1 predose blood draw, which may be taken at any time during the Baseline Visit before the first study treatment administration..."
9.2.13 Urine Testing	--	"…Urine drug screen may include testing for cannabinoids, amphetamines, methamphetamines, cocaine, opiates, benzodiazepines, methaqualone, barbiturates, and phencyclidine based on assays available in trial countries…"
9.3.2 Sputum Assessments for Microbiological Response	"At the baseline visit, three spot sputum specimens will be collected…"	"At the baseline visit, three spot sputum specimens will be collected before the first dose of study treatment is administered…"
9.3.4 Mtb Strain Genotyping	"Mtb strain genotyping will be used to assist in the determination of whether a participant with a positive culture after the completion of treatment has relapsed or been re-infected with another strain of Mtb. Genotyping will be performed on a baseline culture (culture collected at baseline visit or, in rare cases, Week 1) and the first TB-positive culture during the post treatment follow-up period. In addition, the Sponsor may request genotyping at other time points as needed. Further details will be specified in the Laboratory Manual."	"Mtb strain genotyping will be used to assist in the determination of whether a participant with a positive culture at the completion of treatment or after in the post-treatment follow-up period has relapsed or been re-infected with another strain of Mtb. Genotyping will be performed on a baseline culture (culture collected at baseline visit or, in rare cases, Week 1) and the first Mtb-positive culture occurring from the end of treatment study visit through the end of the post treatment follow-up period. In addition, the Sponsor may request genotyping at other time points as needed. Further details will be specified in the Laboratory Manual."
9.3.5, 9.5.1.2, and 9.5.6	9.3.5 Storage of Sputum Pellets and Mtb Isolates "Sputum pellets and Mtb isolates from cultures will be stored for confirmatory DST, future MIC testing, genetic characterization of Mtb, and potential assessment of exploratory endpoints." 9.5.1.2 and 9.5.6 "sputum pellet and Mtb isolate storage…"	9.3.5 Storage of Mtb Isolates "Mtb isolates from cultures will be stored for confirmatory DST, future MIC testing, genetic characterization of Mtb, and potential assessment of exploratory endpoints." 9.5.1.2 and 9.5.6 "sputum pellet" removed
9.4.1 Chest X-Rays	"To assess participant eligibility, a good quality posterior-anterior (PA) CXR will be obtained during the screening period (see Section 6.1, inclusion criteria 4e)."	"To assess participant eligibility, a good quality posterior-anterior (PA) CXR will be obtained during the screening period (see Section 6.1, inclusion criteria 4e). A recently conducted CXR (eg, within 1 week prior to screening) may be used for eligibility determination if the digital CXR file is available."
9.5.3 Follow-Up Period	"Mtb strain genotyping will be performed on the first positive culture for Mtb collected during the follow-up period for comparison with strain genotyping results from baseline. This comparison will assist in the determination of	"Mtb strain genotyping will be performed on the first positive culture for Mtb collected from the end of treatment study visit through the end of the post treatment follow-up period for comparison with strain genotyping results from baseline. This comparison will assist in the determination of whether a participant

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	whether a participant with a positive Mtb culture after the completion of treatment has relapsed or been re-infected with Mtb…"	with a positive Mtb culture at the end of treatment or after has relapsed or been re-infected with Mtb…"
9.5.4 Procedures for Participant with Suspected or Confirmed Poor Treatment Response	"When a participant with a possible poor treatment response is identified, the following investigations should be conducted even if they are not part of the regularly scheduled assessments and procedures for that trial visit:…"	"When a participant with a possible or confirmed poor treatment response is identified, a poor treatment response (PTR) visit should be initiated, and the following investigations should be conducted even if they are not part of the regularly scheduled assessments and procedures for the scheduled trial visit:.." "If a participant is identified to have a potential or confirmed poor treatment response between their regularly scheduled trial visits (eg, based on a positive sputum culture result received between visits), the Investigator may either conduct the PTR visit at the participant's next scheduled visit or ask the participant to return earlier for an unscheduled visit."
9.5.5 Early Termination Visit	"Any participant withdrawn from the trial before their last scheduled trial visit will be asked to return for an early termination visit. Participants for whom trial treatment is permanently stopped or changed by the Investigator will be asked to undergo this early termination visit within 2 weeks of discontinuing trial treatment regardless of the reason for trial treatment discontinuation…"	"Any participant withdrawn from the trial before their last scheduled trial visit will be asked to return for an early termination visit. ~~Participants for whom trial treatment is permanently stopped or changed by the Investigator will be asked to undergo this early termination visit within 2 weeks of discontinuing trial treatment regardless of the reason for trial treatment discontinuation~~…"
9.5.6	**Post Early Termination Follow-Up** "Participants whose treatment with an assigned trial regimen is permanently discontinued or are withdrawn early from participation in the trial for other reasons should continue to be followed in the trial through 12 months post randomization for outcome determination unless consent for on-going trial participation is withdrawn…" "The following assessments should be completed at post-early termination follow-up visits, if possible:…"	**Follow-Up After Permanent Discontinuation of Trial Treatment** "Participants whose trial treatment is permanently discontinued should continue to be followed in the trial through 12 months post randomization for outcome determination unless consent for on-going trial participation is withdrawn at which time an early termination visit should be conducted…" "The following assessments should be completed at post-treatment discontinuation follow-up visits, if possible:.."
11.3 Primary and Key Secondary Endpoints	• "…Unfavorable outcome status through end of treatment (through 17 weeks for DBOS and PBOS and through 26 weeks for 2HRZE/4HR) in the subset of participants with HIV co infection in each treatment group;…"	• "…Unfavorable outcome status through end of treatment (through 17 weeks for DBOS and PBOS and through 26 weeks for 2HRZE/4HR) and at 12 months post randomization in the subset of participants with HIV co infection in each treatment group;…"
11.3.1 Definition of Unfavorable Outcome Status	"In Stage 1, for the primary efficacy endpoint, unfavorable outcome status will be assessed throughout and at the end of treatment (4 months for DBOS and PBOS arms, 6 months for 2HRZE/4HR arm) to inform the decision to proceed to Stage 2…"	"Stage 1 unfavorable outcome status at cross-sectional time points and at the end of treatment (4 months for DBOS and PBOS arms, 6 months for 2HRZE/4HR arm) will inform the decision to proceed to Stage 2…"
13.2.1 Regulatory and Ethical Considerations	• "Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants."	• "Any amendments to the protocol, ICF, and other relevant documents will require IRB/IEC review and approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants. Amendments to the protocol, ICF, and other relevant documents will also be submitted for review and approval to

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		other bodies, such as local regulatory authorities, in accordance with applicable national and local laws and regulations before implementation."
13.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information	• "…Information will be recorded on the appropriate CRF/EDC section and submitted to the Sponsor within 24 hours of learning of a participant's or participant's partner's pregnancy through specific EDC page or emailed/faxed Pregnancy Form if EDC is not available…"	• "…Information will be recorded on the appropriate forms and submitted to the Sponsor within 24 hours of learning of a participant's or participant's partner's pregnancy via email/fax…"

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Title Page		Added Amendment number and date
Sponsor Signatory	Contained line for signature of Head of Therapeutics Development only	Added Head of Biometrics & Data Management and Chief Medical Officer as signatories to comply with updated Gates MRI protocol development SOP
Principal Investigator Signature Page	Not in original version	"Principal Investigator Signature Page "added with PI responsibilities listed and space for PI's signature and institutional affiliation provided
List of Abbreviations		"RMM" abbreviation added for "Relapsing Mouse Model"
1.2 Rationale	Among those infected, approximately 10 million people develop active TB each year. In 2019, 1.4 million people died from TB, making it among the leading infectious disease killers in the world (World Health Organization [WHO], 2020 Report). With the current global coronavirus disease-2019 (COVID-19) pandemic resulting in substantial disruptions to TB health services since early 2020 and the consequent increase in vulnerability to TB, TB incidence, and especially TB mortality, the WHO estimates that one-half million more people may have died from TB in 2020 alone due to the negative effects of the pandemic on global TB control. TB incidence and mortality are projected to increase by around 5% to 15% over the next 5 years, amounting to hundreds of thousands of additional TB deaths worldwide (McQuaid et al, 2021).	Among those infected, approximately 10 million people develop active TB each year. In 2020, 1.5 million people died from TB, making it among the leading infectious disease killers in the world (World Health Organization [WHO], 2021a). With the global coronavirus disease-2019 (COVID-19) pandemic resulting in substantial disruptions to TB health services since early 2020 and the consequent increase in vulnerability to TB, TB incidence, and especially TB mortality, the WHO estimates that one-half million more people may have died from TB in 2020 alone due to the negative effects of the pandemic on global TB control. TB incidence and mortality are projected to increase by around 5% to 15% through 2025, amounting to hundreds of thousands of additional TB deaths worldwide (McQuaid et al, 2021).
1.2 Rationale	this treatment regimen was first introduced as the SOC more than 40 years ago (WHO Treatment Guidelines for National TB Programs, 2020; Nahid, 2016).	this treatment regimen was first introduced as the SOC more than 40 years ago (WHO, 2017a; Nahid et al, 2016).
	…with on-going transmission of the disease (WHO 2017). The treatment increases in complexity and duration (up to 18 months in length) for patients infected with rifampicin-resistant (RR)/MDR Mtb strains.	…with on-going transmission of the disease (WHO, 2017a). The treatment increases in complexity and duration (up to 18 months in length) for patients infected with rifampicin-resistant (RR)/MDR Mtb strains (WHO, 2020).
1.3 Trial Design	The design includes a structured and systematic capture of clinical, safety, microbiologic, and radiographic elements to support an Investigator's assessment and decision to stop treatment after 4 months in the experimental	The design includes a structured and systematic capture of clinical, safety, microbiologic, and radiographic elements to support an Investigator's assessment and decision to stop treatment after 4 months in the experimental arms, or after 6

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	arms, after 6 months in the SOC arm, and watch for post-treatment disease relapse (traditional end point for Phase 3 TB treatment trial); this approach to assessing the stop-treatment-and-watch (StrAW) decision is designed to promote consistency across sites. The dynamics of treatment response over the 4-month period in the experimental arms and over the 6 months of treatment in the control arm will be closely evaluated in Stage 1 to determine acceptability for advancement to and evaluation of shorter treatment durations in Stage 2.	months in the SOC arm, and watch for post-treatment disease relapse (traditional endpoint for Phase 3 TB treatment trial); this approach to assessing the stop-treatment-and-watch (StrAW) decision is designed to promote consistency across sites. The dynamics of treatment effect over the 4-month period in the experimental arms and over the 6 months of treatment in the control arm will be closely evaluated in Stage 1 to determine acceptability for advancement to and evaluation of shorter treatment durations in Stage 2.
1.3 Trial Design	At the end of Stage 1 (when the last participant of the projected enrollment has at least reached the end of treatment), each of the DBOS and PBOS regimens will be assessed for meaningful treatment shortening potential in DS-TB participants down to at most 4 months' duration based on a model characterizing the time course of response and performance criteria (see Section 1.3.3 and Section 11.3.1). If neither DBOS nor PBOS meet the go/no-go performance criteria, the trial will stop and neither regimen will advance to Stage 2. If only one of the DBOS or PBOS regimens meets the performance criteria, the trial will be considered for proceeding to Stage 2 with that regimen (referred to hereafter as 'XBOS'). If both DBOS and PBOS meet the performance criteria, the regimen that is considered to proceed to Stage 2…	At the end of Stage 1 (when the last participant of the projected enrollment has at least reached the end of treatment), each of the DBOS and PBOS regimens will be assessed for treatment shortening potential (≤3 months) in DS-TB participants, which will be characterized by the proportion of participants with unfavorable status at Week 17 for DBOS and PBOS and Week 26 for 2HRZE/4HR as well as truncated unfavorable outcome rates at milestone timepoints for each treatment group (see Section 1.3.3 and Section 11.3.1). Because unfavorable status has a composite definition, summaries will also show which individual components of the composite outcome were met. The Stage 1 efficacy and safety results will be reviewed comprehensively to assess treatment shortening potential and benefit/risk. If neither DBOS nor PBOS shows evidence of treatment shortening potential with an acceptable safety profile, the trial will stop and neither regimen will advance to Stage 2. If only one of the DBOS or PBOS regimens shows evidence of treatment shortening potential with an acceptable safety profile, the trial will be considered for proceeding to Stage 2 with that regimen (referred to hereafter as 'XBOS'). If both DBOS and PBOS show evidence of treatment shortening potential with acceptable safety profiles, the regimen that is considered to proceed to Stage 2…
1.3.1 Trial Schema	• Go/no-go decision to proceed to Stage 2 based on favorable/unfavorable outcome trajectory of DBOS, PBOS vs HRZE through 4, 4, and 6 months of treatment, respectively. • "Eligible Subjects…" • XBOS MDR-TB Obs.	• Decision to proceed to Stage 2 will be based on a comprehensive review of efficacy and safety results of DBOS, PBOS, and HRZE through 4, 4, and 6 months of treatment, respectively • "Eligible Participants…" • XBOS MDR-TB Observational Cohort
1.3.2 Overall Design	• the treatment shortening potential based on the efficacy and safety of the combination regimens of DBOS and PBOS, administered for 4 months, in participants with pulmonary DS-TB in comparison with the 2HRZE/4HR regimen as assessed by the time course of response during treatment, as well as durable cure assessed at the end of 12 months post-randomization (Stage 1) • the efficacy and safety of varying durations of administration (in the range of 2 to 4 months) of the combination regimen of DBOS or PBOS in participants with pulmonary DS-TB in comparison with the 2HRZE/4HR regimen as well as durable cure assessed at the end of 12 months post-randomization (Stage 2)	• the treatment shortening potential based on the efficacy and safety of the combination regimens of DBOS and PBOS, administered for 4 months, in participants with pulmonary DS-TB in comparison with the 2HRZE/4HR regimen as assessed by unfavorable outcome status through end of treatment and through 12 months of post-randomization follow-up, as well as sustained sputum culture conversion to negative assessed during the treatment period and at 12 months of post-randomization follow-up (Stage 1) • the efficacy and safety of varying durations of administration (in the range of 2 to 4 months) of the combination regimen of DBOS or PBOS in participants with pulmonary DS-TB in comparison with the 2HRZE/4HR regimen as well as sustained sputum culture conversion to negative assessed at the end of 12 months post-randomization (Stage 2)

<table>
<tr><th>Section Number</th><th>Text in Version 1</th><th>Text in Version 2 (Amendment 1)</th></tr>
<tr><td>1.3.2 Overall Design</td><td>For Stage 1, the treatment shortening potential of the experimental regimens will be based primarily on the time course of unfavorable treatment outcome status occurring relative to 2HRZE/4HR. The assessment of treatment outcome status will rely on clinical, radiographic, and microbiological response during and at the end of the 4-month (17 weeks) treatment period compared with 2HRZE/4HR during and at the end of 6 months (26 weeks). A regression model will be used to characterize the time course of unfavorable outcome status over the treatment period. Microbiological response will be assessed by sustained sputum culture conversion (SCC) from growth of Mtb to no growth as defined by 2 successive negative cultures at least 1 week apart. The time required to achieve SCC will also be assessed.
Early data regarding post-treatment relapse (see Section 11.3.1 for definition) occurring…</td><td>For Stage 1, the treatment shortening potential of the experimental regimens relative to 2HRZE/4HR will be based primarily on unfavorable treatment outcome status. The assessment of treatment outcome status will rely on clinical, radiographic, and microbiological response during and at the end of the 4-month (17 weeks) treatment period compared with 2HRZE/4HR during and at the end of 6 months (26 weeks). In addition to evaluating the status at end of treatment, unfavorable status based on truncated data at earlier milestone time points will be summarized to create snapshots of unfavorable outcome rates across time for each treatment group. Microbiological response will be assessed by sustained sputum culture conversion (SCC) from growth of Mtb to no growth as defined by 2 successive negative cultures at least 1 week apart. The time required to achieve SCC will also be assessed.
Early data regarding post-treatment relapse occurring…</td></tr>
<tr><td>1.3.5 Number of Participants</td><td>Stage 1 (N=129)
In Stage 1, the trial will enroll approximately 129 participants. The screening period will last up to 10 days. A subgroup of HIV-infected participants (up to approximately 20% of total enrollment) will be enrolled; it is expected that most of these participants will be in South Africa because HIV co-infection is highly prevalent in South Africa but not in other countries planned for trial participation.
…
Stage 2 (N = 385)</td><td>Stage 1 (N = approximately 129)
In Stage 1, the trial will enroll approximately 129 participants. The screening period will last up to 10 days. A subgroup of HIV-infected participants (up to approximately 20% of total enrollment) will be enrolled; it is expected that most of these participants will be enrolled in South Africa because HIV co-infection is highly prevalent in South Africa but not in other countries planned for Stage 1 trial participation.
…
Stage 2 (N = approximately 385)</td></tr>
<tr><td>1.3.6 Dosing (Stages 1 and 2)</td><td>Dosing schedule and requirements are presented in Table 1.
…
Dosing will be performed largely on an ambulatory basis. Participants will be instructed to take all trial medications within 1 hour of ingesting food. Hospitalization is not required for the trial but may be necessary based on local TB management guidelines.
Table 1 Stage 1 Dosing Schedule
<table>
<tr><th>Regimen 1*† (Stage 1, Arm 1)</th><th>D
Delamanid</th><th>B
Bedaquiline</th><th>O
OPC-167832</th><th>S
Sutezolid</th></tr>
<tr><td>Dose and Schedule</td><td>300 mg once daily (QD) for treatment duration</td><td>400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment weeks</td><td>30 mg QD for treatment duration</td><td>1200 mg QD for treatment duration</td></tr>
</table></td><td>The dosing schedule and requirements for the investigational regimens (Regimen 1 & Regimen 2) are presented in Table 1a.
For the dosing schedule and requirements for the SOC regimen (Regimen 3), participants will receive HRZE supplied as HRZE tablets (isoniazid 75 mg, plus rifampicin 150 mg, plus pyrazinamide 400 mg, plus ethambutol 275 mg combination tablets) for 8 weeks. Thereafter, those participants will receive HR supplied as HR tablets (isoniazid 75 mg, plus rifampicin 150 mg combination tablets) for the following 18 weeks. A daily supplement of Vitamin B6 will be taken with HRZE and/or HR, per each country's National TB Treatment Guideline.
The daily dose of HRZE and HR will be based on the participant's weight at screening and during treatment as outlined in Table 1b.
…
Dosing will be performed largely on an ambulatory basis. Participants will be instructed to take the component medications of DBOS and PBOS within 1 hour of ingesting food. Participants randomized to 2HRZE/4HR as SOC will be instructed to take the medicines more than 1 hour after ingesting food. Hospitalization is not required for the trial but may be necessary based on local TB management guidelines.
Table 1a Dosing Schedule for Investigational Regimens
<table>
<tr><th>Regimen 1*† (Stage 1, Arm 1)</th><th>D
Delamanid</th><th>B
Bedaquiline</th><th>O
OPC-167832</th><th>S
Sutezolid</th></tr>
</table></td></tr>
</table>

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Regimen 2*† (Stage 1, Arm 2)	P Pretomanid	B Bedaquiline	O OPC-167832	S Sutezolid
Dose and Schedule	200 mg QD for treatment duration	400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment weeks	30 mg QD for treatment duration	1200 mg QD for treatment duration
Standard of Care* (Stage 1, Arm 3)	**H** Isoniazid	**R** Rifampicin	**Z** Pyrazinamide	**E** Ethambutol
Dose and Schedule	HRZE SOC administered QD recommended as the standard of care for DS-TB treatment in the trial countries will be administered per the national TB treatment guidelines applicable for that country			

* All drugs will be dosed 7 days a week unless specified otherwise. †See Section 3.3.1.3 (DBOS) and Section 3.3.2.3 (PBOS) for dose selection rationale.

Text in Version 2 (Amendment 1)

Dose and Schedule	300 mg once daily (QD) for treatment duration	400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment weeks	30 mg QD for treatment duration	1200 mg QD for treatment duration
Regimen 2*† (Stage 1, Arm 2)	**P** Pretomanid	**B** Bedaquiline	**O** OPC-167832	**S** Sutezolid
Dose and Schedule	200 mg QD for treatment duration	400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment weeks	30 mg QD for treatment duration	1200 mg QD for treatment duration

* Dosing occurs 7 days per week unless specified otherwise.
†See Section 3.3.1.3 (DBOS) and Section 3.3.2.3 (PBOS) for dose selection rationale.

Table 1b Dosing Schedule for SOC Regimen

Intensive Phase						
Weight Band	Weight Range (kg)	Number of FDC Tablets Taken Daily*	Number of Milligrams of Component Drugs Administered			
			Isoniazid	Rifampicin	Pyrazinamide	Ethambutol
1	30-37	2	150	150	800	550
2	38-54	3	225	300	1200	825
3	55-70	4	300	450	1600	1100
4	≥71	5	375	600	2000	1375
Continuation Phase						
Weight Band	Weight Range (kg)	Number of FDC Tablets	Number of Milligrams of Component Drugs Administered			
			Isoniazid	Rifampicin		

<table>
<tr><th>Section Number</th><th>Text in Version 1</th><th>Text in Version 2 (Amendment 1)</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th></th><th></th><th>Taken Daily*</th><th></th><th></th></tr>
<tr><td>1</td><td>30-37</td><td>2</td><td>150</td><td>150</td></tr>
<tr><td>2</td><td>38-54</td><td>3</td><td>225</td><td>300</td></tr>
<tr><td>3</td><td>55-70</td><td>4</td><td>300</td><td>450</td></tr>
<tr><td>4</td><td>≥71</td><td>5</td><td>375</td><td>600</td></tr>
</table>
*Fixed dose combination (FDC) of 75mg of isoniazid, 150mg of rifampicin, 400mg of pyrazinamide, and 275mg of ethambutol (HRZE) for the Intensive Phase and 75mg of isoniazid and 150mg of rifampicin (HR) for the Continuation Phase will be utilized. A small supply of individual agents comprising the HRZE regimen will also be available for clinical management needs including reintroduction of individual agents with weight-based dosing following treatment interruption.
* Dosing occurs 7 days per week unless specified otherwise. WHO treatment guidelines from 2010 and national TB treatment guidelines in countries where trial sites are located serve as the basis for the standard of care dosing schedule (WHO, 2010; Philippines Department of Health, 2020; Republic of South Africa Department of Health, 2014; Peru Ministry of Health, 2013).
</td></tr>
<tr><td>1.4 Table 2 Trial Objectives, Estimands, and Endpoints (Primary Efficacy Estimand) (Stage 1 Tale only)</td><td>In the Per Protocol population (Section 1.7.1), the time point during DBOS treatment that results in a proportion unfavorable status equal to the proportion unfavorable status of 2HRZE/4HR at 26 weeks
• In the Per Protocol population, the time point during PBOS treatment that results in a proportion unfavorable status equal to the proportion unfavorable status of 2HRZE/4HR at 26 weeks</td><td>In the Per Protocol population (Section 1.8.1), the proportion of participants with unfavorable status at Week 17 for DBOS and Week 26 for 2HRZE/4HR
In the Per Protocol population, the proportion of participants with unfavorable status at Week 17 for PBOS and Week 26 for 2HRZE/4HR</td></tr>
<tr><td>1.4 Table 2 Trial Objectives, Estimands, and Endpoints (Secondary Efficacy Estimand and Endpoint for MGIT) (Stage 1 and 2 Tables)</td><td>Estimand
○ Difference in mean daily rate of change in sputum culture time to detection (TTD) from Baseline to Week 8 (DBOS minus 2HRZE/4HR and PBOS minus 2HRZE/4HR) as calculated from the area under the TTD vs week curve (AUC).
Endpoint
• Sputum culture time to detection (TTD) curves in MGIT through 8 weeks of treatment</td><td>Estimand
○ Difference in mean daily rate of change in sputum culture time to detection (TTD) from Baseline to Weeks 4, 8, 9, 13, and 17 (DBOS minus 2HRZE/4HR and PBOS minus 2HRZE/4HR) as calculated from the area under the TTD vs week curve (AUC).
Endpoint
• Sputum culture time to detection (TTD) curves in MGIT through 4, 8, 9, 13, and 17 weeks of treatment</td></tr>
<tr><td>1.4 Table 2 Trial Objectives,</td><td>○ [redacted]</td><td>○ [redacted]</td></tr>
</table>

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Estimands, and Endpoints (Exploratory Estimand for [redacted] (Stage 1 and 2 Tables)		
1.5 IDMC	As two of the compounds included in both regimens – OPC-167832 and sutezolid – are investigational and have only been administered for up to 2 weeks in clinical studies in DS-TB patients, regular reviews by the trial's IDMC are planned. IDMC meetings are planned to occur during Stage 1 approximately after one-third, two-thirds, and all of the 129 participants are enrolled (roughly quarterly), after the last Stage 1 participant has completed treatment, and approximately every 3 to 4 months in Stage 2 with ad hoc meetings as needed. … The IDMC may request additional information, or recommend a pause	As two of the compounds included in both regimens – OPC-167832 and sutezolid – are investigational and have only been administered for up to 2 weeks in completed clinical trials in DS-TB patients, regular reviews by the trial's IDMC are planned. IDMC meetings are planned to occur during Stage 1 approximately after one-third, two-thirds, and all of the 129 participants are enrolled (roughly quarterly), after the last Stage 1 participant has completed treatment, and approximately every 3 to 4 months in Stage 2 with ad hoc meetings as needed. … The IDMC may request additional information, or recommend a pause…
1.6 STrAW Concilium (new section – moved from Section 12.2)		The STrAW Concilium will be established for the trial for the following purposes: • Monitor individual trial participants' response to treatment through the review of standardized data reports produced at important time points (these reports will not indicate a participant's assigned treatment regimen). • Provide expert clinical consultation to Investigators on challenging clinical scenarios, including all participants where the Investigator wants to permanently stop one or more trial medications, continue trial treatment past the assigned duration, or restart TB treatment after the completion of trial treatment (see Section 8.3.2 and Section 9.5.4). The STrAW Concilium will be composed of independent experts in TB clinical management with an understanding of mycobacteriology and experience in the conduct of TB clinical trials. Concilium members will be partially blinded to study regimen assignment (see Section 7.3.2).
1.7 SoA Table 3 (Stage 1) and Table 4 (Stage 2)	Footnote "l" (Table 3), Footnote "m" (Table 4) Biochemistry tests include creatinine, blood urea nitrogen, potassium, sodium, chloride, serum bicarbonate, calcium, magnesium, ALT, AST, total and direct bilirubin, alkaline phosphatase, total protein, albumin, and lactate dehydrogenase. Footnote "p" (Table 3) PK samples will be taken on the following schedule for participants randomized to Arms 1 and 2. PK will not be assessed for Arm 3 (2HRZE/4HR). Baseline	New row for "Sputum collection" added under "Sputum Testing" section with footnote "u" Footnote "l" (Table 3), Footnote "m" (Table 4) Biochemistry tests include creatinine, blood urea nitrogen, estimated glomerular filtration rate, potassium, sodium, chloride, serum bicarbonate, calcium, magnesium, ALT, AST, total and direct bilirubin, alkaline phosphatase, total protein, albumin, and lactate dehydrogenase. Footnote "p" (Table 3) PK samples will be taken on the following schedule for participants randomized to Arms 1 and 2. PK will not be assessed for Arm 3 (2HRZE/4HR). Baseline visit (to

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	visit (to serve as predose sample), Week 1 (predose and 2-6 h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6 h postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), and Week 17 (predose) (12 samples per participant).	serve as predose sample), Week 1 (predose and 2-6 h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6 h postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), and Week 17 (predose), Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12 (18 samples per participant). Random post-treatment PK samples will be collected and tested for bedaquiline and its metabolite only.
	Footnote "q" (Table 4) …Baseline visit (to serve as predose sample), Week 1 (predose and 2-6h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6h postdose), Week 11 (predose) except Arm 1, Week 13 (predose) except Arms 1 and 2, Week 15 (predose) except Arms 1-3, and Week 17 (predose) except Arms 1-4 for Week 17 (8-12 samples per participant depending on treatment arm).	Footnote "q" (Table 4) …Baseline visit (to serve as predose sample), Week 1 (predose and 2-6h postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2-6h postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), Week 17 (predose), Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12. (18 samples per participant). Random post-treatment PK samples will be collected and tested for bedaquiline and its metabolite only.
	Footnote "q" (Table 3), Footnote "r" (Table 4) For women of childbearing potential only, serum β-hCG will be collected at the first screening visit. Point-of-care urine pregnancy testing will be done approximately every 3-4 weeks throughout the trial.	Footnote "q" (Table 3), Footnote "r" (Table 4) For women of childbearing potential only, serum β-hCG will be collected at the first screening visit. Point-of-care urine pregnancy testing will be done at the baseline visit and approximately every 3-4 weeks throughout the trial.
	Footnote "s" (Table 3), Footnote "u" (Table 4) Urine isoniazid (INH) testing will be performed only for participants randomized to Arm 3 (2HRZE/4HR) in Stage 1.	Footnote "s" (Table 3), Footnote "u" (Table 4) Microscopic examination for red blood cells, white blood cells, casts, bacteria, and other abnormalities will be performed if urine dipstick is positive for protein, blood, leukocyte esterase, or nitrites or if otherwise indicated. Urine isoniazid (INH) testing will be performed only for participants randomized to Arm 3 (2HRZE/4HR) in Stage 1.
	Footnote "u" (Table 3), Footnote "w" (Table 4) …At visits where sputum [redacted]. See Section 9.3 for further details.	Footnote "u" (Table 3), Footnote "w" (Table 4) …At visits where sputum [redacted]. See Section 9.3 for further details. Note: The number of these X's reflects the number of sputum specimens to be collected at respective timepoints.
	Footnote "v" (Table 3), Footnote "y" (Table 4) Culture isolates will be stored for all positive cultures for DST and genotyping that may be required.	Footnote "v" (Table 3), Footnote "y" (Table 4) Sputum pellets and culture isolates will be stored for all positive cultures for DST, genotyping, and any repeat testing that may be required.

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	Footnote "w" (Table 3), Footnote "z" (Table 4) If baseline visit sputum [redacted] is negative or uninterpretable, [redacted] can be performed on the Week 1 sputum specimen.	Footnote "w" (Table 3), Footnote "z" (Table 4) Footnote deleted
1.8.5 Interim Analysis	An interim analysis will be performed after all Stage 1 participants finish the end of treatment to assess the treatment shortening potential of DBOS and PBOS down to at most 4 months' duration. Continuous monitoring for futility by the IDMC based on the 12-months post-randomization unfavorable outcome rate end point will be implemented in both Stage 1 and Stage 2, after at least 20 participants have been enrolled in each group.	An interim analysis will be performed after all Stage 1 participants have reached the end of treatment to assess the treatment shortening potential of DBOS and PBOS. Regular monitoring for futility by the IDMC based on the 12-months post-randomization unfavorable outcome rate endpoint will be implemented in both Stage 1 and Stage 2, after at least 20 participants have been enrolled in each group.
1.8.6 Sample Size Justification	The operating characteristics of the Stage 1 decision criteria were examined via clinical trial simulation. Five underlying true response profiles of XBOS (DBOS or PBOS) were examined relative to 2HRZE/4HR. In addition, 3 sample sizes (N=30, 40, and 50/group) and 3 sampling strategies (12, 15, or 25 samples collected for each participant) were examined.	In Stage 1, approximately 43 participants per arm will be enrolled in a 1:1:1 randomization ratio to the treatment groups described in Figure 1. The operating characteristics of the Stage 1 decision criteria were examined via simulation under binomial distributions with n=43 per treatment group (see Section 11.7).
2 Introduction	With the current global coronavirus disease-2019 (COVID-19) pandemic resulting in substantial disruptions to TB health services since early 2020 and the consequent increase in vulnerability to TB, TB incidence, and especially TB mortality, the WHO estimates that one-half million more people may have died from TB in 2020 alone due to the negative effects of the pandemic on global TB control, and TB incidence and mortality are projected to increase by around 5% to 15% over the next 5 years, amounting to hundreds of thousands of additional TB deaths worldwide (McQuaid et al, 2021).	With the current global coronavirus disease-2019 (COVID-19) pandemic resulting in substantial disruptions to TB health services since early 2020 and the consequent increase in vulnerability to TB, TB incidence, and especially TB mortality, the WHO estimates that one-half million more people may have died from TB in 2020 alone due to the negative effects of the pandemic on global TB control, and TB incidence and mortality are projected to increase by around 5% to 15% through 2025, amounting to hundreds of thousands of additional TB deaths worldwide (McQuaid et al, 2021).
2.1.1.1 Relapsing Mouse Model	New section	Recent data from an in vivo relapsing mouse model (RMM) study evaluating the DBOS and PBOS regimens support the rationale for TB regimen construction in this trial of adding a fourth anti-TB agent to the proven TB treatment benefit from a backbone regimen of a diarylquinoline, a nitroimidazole, and an oxazolidinone agent. In this study, BALB/c mice were infected with a high-dose aerosol of Mtb Erdman and treated after 11 days with DBOS, PBOS, or one of 2 control regimens: HRZE or the best performing TB regimen to date in RMM studies, BPaMZ (bedaquiline, pretomanid, moxifloxacin, and pyrazinamide). Bactericidal activity was assessed following 2, 4, 6, 8 and 10 weeks of treatment. Relapse prevention was measured using groups of companion mice sacrificed 3 months after cessation of drug therapy. This study incorporated the "Erasmus-Cognigen" design which includes more frequent sampling of smaller numbers of mice and regression analysis and modelling of the resultant data to better calculate true relapse probability and time profiles. From this model, regimens are considered effective when treatment duration is shortened by at least 1-2 months relative to the 6-month HRZE regimen. The results from the study demonstrated that the DBOS, PBOS, and BPaMZ regimens were all more bactericidal than HRZE and no statistically significant

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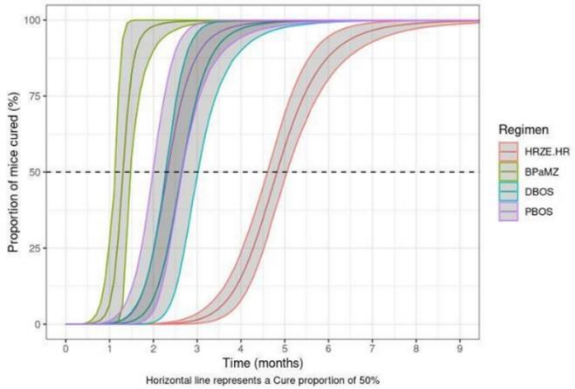
		differences in performance between DBOS or PBOS were detected at any of the timepoints assessed based on bactericidal response. In the study, all regimens showed significant improvement in treatment shortening compared to HRZE which routinely achieves durable cure with no relapse after 5-6 months of therapy in the BALB/c RMM; BPaMZ shortened the time to durable cure by at least 3.5 months, which is consistent with previous RMM studies including that regimen (Xu et al, 2019), and the DBOS and PBOS regimens shortened the time to cure by at least 2.5 months. Of note, the BPaMZ regimen is being evaluated in the Phase 2c SimpliciTB trial administered for 4 months in DS-TB patients and 6 months in DR-TB patients with results expected in 2023 (www.clinicaltrials.gov, NCT03338621). Figure 2 shows the results from the mathematical modelling and regression analysis of the study data, which clearly demonstrates the superiority of DBOS and PBOS compared with HRZE. A model-based meta-analysis approach provided the framework to compare the efficacy of the DBOS, PBOS, BPaMZ, and HRZE treatment regimens (Berg et al, 2022). **Figure 2 Relapse Probability Versus Treatment Duration for DBOS, PBOS, BPaMZ, and HRZE Regimens in BALB/c Relapsing Mouse Model**  *Smooth lines and shaded areas represent the median and 95% confidence intervals.*
3.3.1.2 Supportive Evidence From Combination Evaluation: Delamanid,	As outlined in Section 3.2.1, Otsuka Pharmaceuticals has evaluated the early bactericidal activity of OPC-167832 of varying doses over 14-days in stage one of a two-stage trial (www.clinicaltrials.gov; NCT03678688). This trial has progressed to stage two with an evaluation of 14 days of administration of OPC 167832 in combination with delamanid, with bedaquiline, and with delamanid plus bedaquiline currently underway; trial completion is expected to occur in	As outlined in Section 3.2.1, Otsuka Pharmaceuticals has evaluated the early bactericidal activity of OPC-167832 of varying doses over 14-days in stage one of a two-stage trial (www.clinicaltrials.gov; NCT03678688). This trial has progressed to stage two with an evaluation of 14 days of administration of OPC 167832 in combination with delamanid, with bedaquiline, and with delamanid plus bedaquiline currently underway; the trial has completed with results expected to be available in

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Bedaquiline and OPC 167832	November 2021. Of note, the doses being assessed are OPC 167832 at 30 mg daily, delamanid at 300 mg daily (one of the single daily doses evaluated in the delamanid early bactericidal activity trial referenced in Section 3.1.2 (Diacon et al, 2014) and bedaquiline at 400 mg daily. As reported for Stage 1 in the evaluation of multiple doses of OPC-167832, no serious or severe AEs occurred and no participants were discontinued from the trial due to an AE.	early 2023. Of note, the doses being assessed are OPC 167832 at 30 mg daily, delamanid at 300 mg daily (one of the single daily doses evaluated in the delamanid early bactericidal activity trial referenced in Section 3.1.2 (Diacon et al, 2014) and bedaquiline at 400 mg daily. As reported for Stage 1 in the evaluation of multiple doses of OPC-167832, no serious or severe AEs occurred and no participants were discontinued from the trial due to an AE. A follow-on Phase 2b trial sponsored by Otsuka Pharmaceuticals evaluating OPC-167832 administered as 10 mg, 30 mg, or 90 mg daily in combination with bedaquiline and delamanid for 4 months in patients with DS-TB is currently enrolling in South Africa (www.clinicaltrials.gov; NCT05221502).
3.3.1.3.3 OPC-167832 Dose Selection and Rationale	A separate Phase 2b/c trial evaluating OPC-167832 administered at 10 mg QD, 30 mg QD, or 90 mg QD in combination with delamanid 300 mg QD and bedaquiline 400 mg QD for 2 weeks then 200 mg thrice weekly for 17 weeks total is expected to begin enrolling in early 2022. Available findings from that trial regarding the optimal dose of OPC-167832 will be reviewed to determine if the dose of OPC-167832 should be modified in Stage 2.	As previously noted, a separate Phase 2b/c trial evaluating OPC-167832 administered at 10 mg QD, 30 mg QD, or 90 mg QD in combination with delamanid 300 mg QD and bedaquiline 400 mg QD for 2 weeks then 200 mg thrice weekly for 17 weeks total is currently enrolling (www.clinicaltrials.gov; NCT05221502). Available findings from that trial regarding the optimal dose of OPC-167832 will be reviewed to determine if the dose of OPC-167832 should be modified in Stage 2.
3.3.1.4 Summary for DBOS	The totality of the available non-clinical HFS-TB evidence demonstrating the substantial decrease in time to extinction relative to the control regimen with the DBOS 4-drug combination regimen (see Section 2.1.1)…	The totality of the available non-clinical evidence demonstrating the substantial decrease in time to durable cure in the relapsing mouse TB model and decreased time to extinction in the hollow fiber system with the DBOS 4-drug combination regimen relative to the control regimen (see Section 2.1.1)…
3.4 Overall Conclusions	As reviewed in Section 3.3.1 for DBOS and Section 3.3.2 for PBOS, though these combinations are novel and have not previously been evaluated in the clinic, the available supportive evidence does suggest that these regimens have potential for meaningful treatment shortening. In addition, DBOS evaluated in the HFS-TB model demonstrated added benefit with a progressively faster time to extinction compared to the combinations of delamanid plus bedaquiline plus OPC-167832 and delamanid plus OPC-167832, and time to extinction for this 4-drug combination was nearly one half of the duration for the standard regimen serving as the in-study control (see Section 2.1.1)…	As reviewed in Section 3.3.1 for DBOS and Section 3.3.2 for PBOS, though these combinations are novel and have not previously been evaluated in the clinic, the available supportive evidence does suggest that these regimens have potential for meaningful treatment shortening. Both regimens demonstrated improved bactericidal activity and reduced time to durable cure compared with HRZE in the relapsing mouse TB model. In addition, DBOS evaluated in the HFS-TB model demonstrated added benefit with a progressively faster time to extinction compared to the combinations of delamanid plus bedaquiline plus OPC-167832 and delamanid plus OPC-167832, and time to extinction for this 4-drug combination was nearly one half of the duration for the standard regimen serving as the in-study control (see Section 2.1.1)…
5.1 Overall Trial Design	• Stage 1: the treatment shortening potential based on the safety and efficacy of the combination regimens of DBOS and PBOS, administered for 4 months, in participants with pulmonary DS TB in comparison with the standard 2HRZE/4HR regimen as assessed at the end of treatment • Stage 2: the efficacy and safety of varying durations of administration (in the range of 2 to 4 months) of the combination regimen of DBOS or PBOS in comparison with the standard 2HRZE/4HR regimen as well as durable cure assessed at the end of 12 months post randomization	• Stage 1: the treatment shortening potential based on the safety and efficacy of the combination regimens of DBOS and PBOS, administered for 4 months, in participants with pulmonary DS TB in comparison with the standard 2HRZE/4HR regimen as assessed by the unfavorable outcome status through end of treatment and through 12 months of post-randomization follow-up, as well as sustained sputum culture conversion to negative assessed during the treatment period and the 12 months of post randomization follow-up • Stage 2: the efficacy and safety of varying durations of administration (in the range of 2 to 4 months) of the combination regimen of DBOS or PBOS in comparison with the standard 2HRZE/4HR regimen as well as sustained sputum

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		culture conversion to negative assessed at the end of 12 months post randomization
5.1 Overall Trial Design	For Stage 1, the treatment shortening potential of the experimental regimens will be based on the time course of unfavorable treatment outcome status occurring relative to SOC. The assessment of treatment shortening potential of the experimental regimens will be based on clinical, radiographic, and microbiological response during and at the end of the 4-month (17 weeks) treatment period compared with 6 months (26 weeks) of 2HRZE/4HR. A regression model will be used to characterize the time course of unfavorable outcome status over the treatment period. Microbiological response will be assessed by sustained conversion of sputum culture from growth of Mtb to no growth as defined by 2 successive negative cultures at least 1 week apart. Time to culture conversion will also be assessed. When the last Stage 1 participant has reached the end of treatment, each of the DBOS and PBOS regimens will be assessed for meaningful treatment shortening potential down to at most 4 months' duration using performance criteria (see Section 1.7.4 and Section 11.3.1). If neither DBOS nor PBOS meet the performance criteria, the trial will stop and neither regimen will advance to Stage 2. If only one of the DBOS or PBOS regimens meets the performance criteria, that regimen will be considered for proceeding to Stage 2. If both DBOS and PBOS meet the performance criteria, the regimen that is considered for proceeding to Stage 2 will be the one with the more favorable profile overall, including, but not limited to, an assessment of secondary efficacy end points, which incorporate data on post-treatment relapses, safety, tolerability, and alignment with the target regimen profile for a new, affordable, shorter, safer, and simpler TB treatment regimen to treat all TB patients regardless of drug resistance status.	For Stage 1, the treatment shortening potential of the experimental regimens relative to 2HRZE/4HR will be based on unfavorable treatment outcome status. The assessment of treatment shortening potential of the experimental regimens will be based on clinical, radiographic, and microbiological response during and at the end of the 4-month (17 weeks) treatment period compared with 6 months (26 weeks) of 2HRZE/4HR. In addition to evaluating the status at end of treatment, unfavorable status based on truncated data at earlier milestone time points will be summarized to create snapshots of unfavorable outcome rates across time for each treatment group. Microbiological response will be assessed by sustained conversion of sputum culture from growth of Mtb to no growth as defined by 2 successive negative cultures at least 1 week apart. Time to culture conversion will also be assessed. When the last Stage 1 participant has reached the end of treatment, each of the DBOS and PBOS regimens will be assessed for treatment shortening potential in DS-TB participants, which will be characterized by the proportion of participants with unfavorable status at Week 17 for DBOS and PBOS and Week 26 for 2HRZE/4HR as SOC as well as truncated unfavorable outcome rates at milestone timepoints for each treatment group (see Section 1.8.4 and Section 11.3.1). Because unfavorable status has a composite definition, summaries will also show which individual components of the composite outcome were met. The Stage 1 efficacy and safety results will be reviewed comprehensively to assess treatment shortening potential and benefit/risk. . If neither DBOS nor PBOS shows evidence of treatment shortening potential with an acceptable safety profile, the trial will stop and neither regimen will advance to Stage 2. If only one of the DBOS or PBOS regimens shows evidence of treatment shortening potential with an acceptable safety profile, that regimen will be considered for proceeding to Stage 2. If both DBOS and PBOS show evidence of treatment shortening potential with acceptable safety profiles, the regimen that is considered for proceeding to Stage 2 will be the one with the more favorable profile overall, including, but not limited to, an assessment of secondary efficacy endpoints, which incorporate data on post-treatment relapses, safety, tolerability, and alignment with the target regimen profile for a new, affordable, shorter, safer, and simpler TB treatment regimen to treat all TB patients regardless of drug resistance status.
5.2 Justification for Dose	See Section 3.3.1.3 and Section 3.3.2.3 for justification of DBOS and PBOS dosing, respectively.	See Section 3.3.1.3 and Section 3.3.2.3 for justification of DBOS and PBOS dosing, respectively. WHO treatment guidelines from 2010 (which remain current for 2022) and current national TB treatment guidelines in the countries where trial sites are located serve as the basis for dosing of each anti-TB drug comprising the SOC regimen (2HRZE/4HR) as featured in Section 1.3.6, Table 1b (WHO, 2010; WHO, 2017a; Peru Ministry of Health, 2013; Philippines Department of Health, 2020; Republic of South Africa Department of Health, 2014).

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6.1 Inclusion Criteria	Criteria 4a Confirmation of Mtb infection: Mtb positivity on a molecular test (eg, Xpert Ultra, Hain LPA) conducted on a sputum specimen Criteria 4c Drug-susceptible TB: Isoniazid and rifampicin resistance not detected, as determined by a molecular test (eg, Hain LPA, Xpert Ultra, Xpert MTB/XDR) conducted on a sputum specimen	Criteria 4a Confirmation of Mtb infection: Mtb positivity on a molecular test (eg, Xpert Ultra, Hain LPA) conducted on a sputum specimen for trial screening Criteria 4c Drug-susceptible TB: Isoniazid and rifampicin resistance not detected, as determined by a molecular test (eg, Hain LPA, Xpert Ultra, Xpert MTB/XDR) conducted on a sputum specimen for trial screening
6.2 Exclusion Criteria	Criteria 9d Evidence of a currently active opportunistic malignancy or infection related to HIV other than TB (oral candidiasis is not exclusionary). 15a Estimated creatinine clearance <60 mL/min Similarly, participants randomized to the 2HRZE/4HR arm whose baseline phenotypic DST results demonstrate resistance to isoniazid and/or rifampicin will not be included in efficacy analyses.	Criteria 9d Evidence of a currently active opportunistic malignancy or infection related to HIV other than TB that requires treatment with a prohibited concomitant medication (oral candidiasis is not exclusionary). 15a Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 DS-TB participants whose baseline phenotypic DST results demonstrate resistance to isoniazid and/or rifampicin will not be included in efficacy analyses.
6.4 Screening	New parent 6.4 section	Screening assessments can be done at any time during the screening window except for written informed consent, which must be completed prior to any screening procedure.
6.4.2 Re-screening (new sub-section)	Investigators may review rescreening eligibility on a case-by-case basis with the Sponsor.	Screening procedures may be repeated if there are technical or operational difficulties with collection, processing, or running of screening laboratory tests (e.g., laboratory reports hemolyzed blood or sputum container leaks) or conducting a screening procedure (e.g., ECG machine error) if the repeat screening procedure can be completed within the original screening window. Investigators may review rescreening eligibility on a case-by-case basis with the Sponsor.
7.1.1 Investigational Agents Composition and Administration	The commercially marketed investigational products (delamanid, pretomanid, bedaquiline) will be packaged/repackaged in blisters or bottles consistent with their commercially marketed presentations in the country/region from where they are sourced.	The commercially marketed investigational products (delamanid, pretomanid, bedaquiline) will be packaged/repackaged in blisters or bottles as needed to support this clinical trial.
7.1.2 Management of Investigational Product	Trial drugs will be dispensed in an unmasked (unblinded) fashion based on the randomization list by authorized and trained site staff members.	The trial's investigational drugs will be dispensed in an unmasked (unblinded) fashion based on the randomization list by authorized and trained site staff members.
7.1.3 Management of		**New section**

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Standard of Care		The 2HRZE/4HR combination is approved, indicated, and commonly used as a 6-month treatment for DS-TB patients. Participants randomized to the 2HRZE/4HR control arm in this trial will be given standard weight-adjusted doses of HRZE. See the HRZE package insert for more information (Rimstar SmPC, 2021) and Table 1b. A small supply of individual agents comprising 2HRZE/4HR will also be available for clinical management needs including reintroduction of individual agents with weight-based dosing following treatment interruption.
7.3.2 Masking (Blinding)	This trial will be open label for trial participants, trial site personnel, IDMC members, and Sponsor and CRO personnel. Microbiology lab personnel will be blinded to trial treatment.	This trial will be open label for trial participants, trial site personnel, IDMC members, and Sponsor and CRO personnel. Microbiology lab personnel will be blinded to all trial participants' treatment assignments. STrAW Concilium members will be blinded to the specific regimen assignment among those randomized to receive an investigational regimen. It is not feasible to blind Concilium members from whether a participant was assigned an investigational regimen or standard of care due to their different durations of treatment and intensive and continuation phases for 2HRZE/4HR (see Section 1.6).
7.4 Trial Intervention ~~Compliance~~ Adherence	Dosing will be performed largely on an ambulatory basis. Participants will be instructed to take all study medications within 1 hour of ingesting food. Dosing schedule and requirements for Stage 1 are presented in Table 1. Dosing schedule for Stage 2 for the regimen chosen to move forward with be the same as Stage 1, but duration will vary according to assigned arm (see Section 7.3.1).	Dosing will be performed largely on an ambulatory basis. Participants will be instructed to take the component medications of DBOS and PBOS within 1 hour of ingesting food. Participants randomized to 2HRZE/4HR will be instructed to take the medicines more than 1 hour after ingesting food. Dosing schedule and requirements for Stage 1 are presented in Table 1a. Dosing schedule for Stage 2 for the regimen chosen to move forward with be the same as Stage 1, but duration will vary according to assigned arm (see Section 7.3.1).
7.5 Prior and Concomitant Therapy or Medications	Participants assigned to 2HRZE/4HR will be prescribed pyridoxine (vitamin B6) 25 mg daily throughout their treatment to reduce the risk of peripheral neuropathy from isoniazid. This preventative measure is recommended by WHO and national TB programs. Pyridoxine does not have any drug-drug interactions of concern with any study drugs. Participants assigned to the DBOS and PBOS arms do not require co-administration of pyridoxine due to the different mechanism by which oxazolidinones are believed to induce peripheral neuropathy (see Section 3.2.2.2.1). Receipt of COVID-19 vaccination during trial participation will also be collected through concomitant medication review.	Participants assigned to 2HRZE/4HR should be prescribed pyridoxine (vitamin B6) to reduce the risk of peripheral neuropathy from isoniazid as per the applicable local or national guidelines where they are enrolled. This preventative measure is recommended by WHO and most national TB programs. Pyridoxine does not have any drug-drug interactions of concern with any study drugs. Participants assigned to the DBOS and PBOS arms do not require co-administration of pyridoxine due to the different mechanism by which oxazolidinones are believed to induce peripheral neuropathy (see Section 3.2.2.2.1), but the Investigator is permitted to prescribe it based on their clinical judgement. Receipt of COVID-19 vaccination during trial participation will also be collected through concomitant medication review.
7.6 Dose Modification	The dose of 2HRZE/4HR should be adjusted, as needed, for the participant's current weight recorded at the most recent trial visit according to each site's national TB treatment guidelines.	The dose of 2HRZE/4HR should be adjusted, as needed, for the participant's current weight recorded at the most recent trial visit per the dosing guidance in Section 1.3.6.
8.3.1.1 General Guidance on Treatment Interruption	Sequential reintroduction of study drugs (and essential concomitant medications) should be considered when it is not clear which drug, if any, caused the toxicity.	Sequential reintroduction of study drugs, including SOC, (and essential concomitant medications) should be considered when it is not clear which drug, if any, caused the toxicity.
8.3.2 Permanent Discontinuation	Randomized participants who meet one or more of the following criteria will be discontinued from trial treatment: • Pregnancy	Randomized participants who meet one or more of the following criteria will be discontinued from trial treatment: • Pregnancy

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of Trial Treatment	• Participant request for permanent discontinuation of trial treatment • Any clinical adverse event, laboratory abnormality, intercurrent medical condition or illness, new requirement for a concomitant medication on the excluded medication list, or other situation where an Investigator determines that continued administration of trial treatment is not in the best interest of the participant • Treatment failure based on Investigator judgement (with STrAW Concilium consultation, see Section 12.2) • For participants randomized to 2HRZE/4HR arm only: Baseline sputum culture drug susceptibility testing demonstrates resistance to rifampicin and/or isoniazid (Note: all DS TB participants require screening results documenting no resistance identified to rifampicin and isoniazid prior to randomization). These participants should be referred to their local DR-TB program for appropriate management. Participants randomized to DBOS or PBOS who are subsequently found to have rifampicin or isoniazid resistance will remain on their assigned regimen since presence of rifampicin or isoniazid resistance does not affect the anti-TB activity of agents in DBOS and PBOS. Participants found to be resistant to pyrazinamide or ethambutol are not required to change their treatment regardless of whether they are receiving 2HRZE/4HR, DBOS, or PBOS. Investigators should discuss decisions regarding the permanent discontinuation of one or more trial medications for a participant with the STrAW Concilium and inform the Sponsor. See Section 9.5.4 for further details of management of participants permanently discontinued from trial treatment.	• Participant request for permanent discontinuation of trial treatment • Any clinical adverse event, laboratory abnormality, intercurrent medical condition or illness, new requirement for a concomitant medication on the excluded medication list, or other situation where an Investigator determines that continued administration of trial treatment is not in the best interest of the participant • Treatment failure based on Investigator judgement (with STrAW Concilium consultation, see Section 1.6) • For participants randomized to 2HRZE/4HR arm only: Baseline sputum culture phenotypic drug susceptibility testing demonstrates resistance to rifampicin and/or isoniazid (Note: all DS TB participants require screening results documenting no resistance identified to rifampicin and isoniazid on rapid molecular test(s) prior to randomization). These participants should be referred to their local DR-TB program for appropriate management. Participants randomized to DBOS or PBOS who are subsequently found to have rifampicin or isoniazid resistance may remain on their assigned regimen since presence of rifampicin or isoniazid resistance does not affect the anti-TB activity of agents in DBOS and PBOS. Participants found to be resistant to pyrazinamide or ethambutol are not required to change their treatment regardless of whether they are receiving 2HRZE/4HR, DBOS, or PBOS. Removed: • ~~For participants enrolled to RR/MDR TB arm only: If baseline sputum culture phenotypic drug susceptibility testing demonstrates resistance to fluoroquinolones, the participant may remain in the trial on their XBOS regimen if they agree after discussion with the Investigator (Note: all RR/MDR TB participants require screening results documenting no fluoroquinolone resistance detected on rapid molecular test(s) prior to enrolment).~~ Investigators should discuss decisions regarding the permanent discontinuation of one or more trial investigational medications for a participant with the STrAW Concilium and inform the Sponsor (see Section 1.6). See Section 9.5.4 for further details of the evaluation and management of participants permanently discontinued from trial treatment.
8.4 Lost to Follow-up	Acceptable documentation of life includes direct contact with the participant, medical records, successful phone contact with the participant, public records, and statements by a family member or physician.	Acceptable documentation of life includes, but is not limited to, direct contact with the participant, medical records, successful phone contact with the participant, public records, and statements by a family member or physician.
9.2.1 Hematology	Reticulocyte count will also be measured to monitor for signs of myelosuppression, which is a class effect of oxazolidinones to which sutezolid belongs, although myelosuppression has not been associated with sutezolid in nonclinical and clinical studies conducted to date.	Reticulocyte count will also be measured to monitor for signs of myelosuppression, which is a class effect of oxazolidinones to which sutezolid belongs, although myelosuppression has not been associated with sutezolid in nonclinical and clinical studies conducted to date (see Section 3.2.2.2.1).

<table>
<tr><th>Section Number</th><th>Text in Version 1</th><th>Text in Version 2 (Amendment 1)</th></tr>
<tr><td>9.2.2 Biochemistry</td><td>Blood will be drawn at screening for measurement of creatinine, blood urea nitrogen, potassium, sodium, chloride, serum bicarbonate, calcium, magnesium, ALT, AST, total and direct bilirubin, alkaline phosphatase, total protein, albumin, creatine kinase, lactate dehydrogenase, and C-reactive protein (CRP) and repeated at regular intervals throughout the trial.</td><td>Blood will be drawn at screening for measurement of creatinine, blood urea nitrogen, potassium, sodium, chloride, serum bicarbonate, calcium, magnesium, ALT, AST, total and direct bilirubin, alkaline phosphatase, total protein, albumin, creatine kinase, lactate dehydrogenase, and C-reactive protein (CRP) and repeated at regular intervals throughout the trial. Estimated glomerular filtration rate will be calculated from serum creatinine.</td></tr>
<tr><td>9.2.8 Pregnancy Testing</td><td>Post randomization, point-of-care urine β-hCG testing will be conducted approximately every 3 to 4 weeks at trial visits for all participants who are FOCBP until 12 weeks after last dose of trial drug.</td><td>Point-of-care urine β-hCG testing will also be conducted at the baseline visit and approximately every 3 to 4 weeks post-randomization at trial visits for all participants who are FOCBP until 12 weeks after last dose of trial drug.</td></tr>
<tr><td>9.2.10 PK Sampling</td><td>• Baseline visit (Day 1) (to serve as predose sample), Week 1 (predose and 2 to 6 hours postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2 to 6 hours postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), and Week 17 (predose) (12 samples per participant)
• If a participant undergoes an Early Termination visit while they are on trial treatment, samples for PK should be collected. Ideally, predose and 2 to 6-hour postdose samples should be collected, but a single random sample is acceptable.

For Stage 2, the following time points will be assessed for Arms 1 to 5 and the RR/MDR-TB cohort (8 to 12 samples per participant depending on treatment arm):</td><td>• Baseline visit (Day 1) (to serve as predose sample), Week 1 (predose and 2 to 6 hours postdose), Week 2 (predose), Week 4 (predose), Week 6 (predose), Week 9 (predose and 2 to 6 hours postdose), Week 11 (predose), Week 13 (predose), Week 15 (predose), Week 17 (predose), Week 19, Week 21, Week 23, Week 26, Month 9, and Month 12 (18 samples per participant)
• Post-treatment PK samples will be collected and tested for bedaquiline and its metabolite only.
• If a participant undergoes an Early Termination visit while they are on trial treatment, samples for PK should be collected. Ideally, predose and 2 to 6-hour postdose samples should be collected, but a single random sample is acceptable.

For Stage 2, Table 11 details the following time points that will be assessed for Arms 1 to 5 and the RR/MDR-TB cohort (18 samples per participant).</td></tr>
<tr><td>9.2.10 Stage 2 PK Sampling Table</td><td colspan="2">
<table>
<tr><th>XBOS Arm</th><th>Day 1</th><th>Week 1</th><th>Week 2</th><th>Week 4</th><th>Week 6</th><th>Week 9</th><th>Week 11</th><th>Week 13</th><th>Week 15</th><th>Week 17</th></tr>
<tr><td>1</td><td>Pre-dose</td><td>Predose and 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td><td>Predose & 2-6 hr postdose</td><td>Random</td><td>Random</td><td>Random</td><td>Random</td></tr>
<tr><td>2</td><td>Pre-dose</td><td>Predose and 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td><td>Predose & 2-6 hr postdose</td><td>Pre-dose</td><td>Random</td><td>Random</td><td>Random</td></tr>
<tr><td>3</td><td>Pre-dose</td><td>Predose and 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td><td>Predose & 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Random</td><td>Random</td></tr>
<tr><td>4</td><td>Pre-dose</td><td>Predose and 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td><td>Predose & 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td><td>Random</td></tr>
<tr><td>5</td><td>Pre-dose</td><td>Predose and 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td><td>Predose & 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td></tr>
<tr><td>RR/ MDR-TB cohort</td><td>Pre-dose</td><td>Predose and 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td><td>Predose & 2-6 hr postdose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td><td>Pre-dose</td></tr>
<tr><td>XBOS Arm</td><td>Week 19</td><td colspan="2">Week 21</td><td>Week 23</td><td>Week 26</td><td colspan="2">Month 9</td><td colspan="2">Month 12</td></tr>
<tr><td>1-5</td><td>Random</td><td colspan="2">Random</td><td>Random</td><td>Random</td><td colspan="2">Random</td><td colspan="2">Random</td></tr>
<tr><td>RR/ MDR-TB</td><td>Random</td><td colspan="2">Random</td><td>Random</td><td>Random</td><td colspan="2">Random</td><td colspan="2">Random</td></tr>
</table>
</td></tr>
</table>

Section Number	Text in Version 1	Text in Version 2 (Amendment 1)
	cohort [redacted]	
9.2.10 PK Sampling	The predose blood draw should be drawn approximately 15 minutes prior to the daily dose of DBOS or PBOS. The postdose blood draw should be done at a flexible time approximately 2 to 6 hours postdose. If a PK blood sample cannot be drawn at the designated time, a window of ±15 minutes for each blood draw is acceptable, with the exact time recorded.	The predose blood draw should be drawn approximately 15 minutes prior to the daily dose of DBOS or PBOS. The postdose blood draw should be done at a flexible time approximately 2 to 6 hours postdose. If a PK blood sample cannot be drawn at the designated time, a window of ±15 minutes for each blood draw is acceptable, with the exact time recorded. Post-treatment PK samples will be collected and tested for bedaquiline and its metabolite only.
9.2.13 Urine Testing	Urine will be collected at screening for urinalysis (dipstick and microscopy) and urine drug screen for trial eligibility determination (see Section 6.2). Urine will be collected for urine INH testing at Weeks 4, 9, 13, 17, 21, and 26 for participants randomized to 2HRZE/4HR (Arm 3 of Stage 1, Arm 6 of Stage 2) to confirm adherence. [redacted]	Urine will be collected at screening for urinalysis (dipstick and reflex microscopy) and urine drug screen for trial eligibility determination (see Section 6.2). Urine dipstick will test for pH, specific gravity, glucose, protein, blood, leukocyte esterase, nitrites, ketones, bilirubin, and urobilinogen. Microscopic examination for red blood cells, white blood cells, casts, bacteria, and other abnormalities will be performed if urine dipstick is positive for protein, blood, leukocyte esterase, or nitrites or if otherwise indicated. Urine will be collected for urine INH testing at Weeks 4, 9, 13, 17, 21, and 26 for participants randomized to 2HRZE/4HR (Arm 3 of Stage 1, Arm 6 of Stage 2) to confirm adherence. [redacted]
9.2.14 SARS-CoV-2 Testing	It will also be performed at suspected poor treatment response and early termination visits unless the reason for an early termination is pregnancy or withdrawal of consent.	It will also be performed at suspected poor treatment response (see Section 9.5.4) and early termination visits (see Section 9.5.5) unless the reason for an early termination is pregnancy or withdrawal of consent.
9.3.1 Screening Sputum for Eligibility	• LPA and/or Xpert MTB/XDR does not detect resistance to INH and RIF and Xpert Ultra does not detect RIF resistance (if Xpert Ultra was previously performed) … • Either smear is AFB-positive at a grade of ≥1+ as defined on the IUATLD/WHO scale or Xpert Ultra result demonstrates Mtb detected with a semi-quantitative Ct result of 'medium' or 'high' on the sputum specimen collected for trial screening, AND • LPA and/or Xpert MTB/XDR detects resistance to RIF (± INH) and/or Xpert Ultra detects resistance to RIF (if Xpert Ultra was previously performed), AND • LPA and/or Xpert MTB/XDR does not detect resistance to fluoroquinolones In both stages, if testing is inconclusive from the first screening sputum specimen, a second sputum can be collected during the screening period. Screening sputum testing details are provided in the Microbiology Laboratory Manual.	• Results from any combination of LPA, Xpert Ultra, or Xpert MTB/XDR do not detect resistance to INH and RIF. …. • Either smear is AFB-positive at a grade of ≥1+ as defined on the IUATLD/WHO scale or Xpert Ultra result demonstrates Mtb detected with a semi-quantitative result of 'medium' or 'high' on the sputum specimen collected for trial screening, AND • Results from any combination of LPA, Xpert Ultra, or Xpert MTB/XDR detect resistance to RIF (± INH), AND • Results from any combination of LPA and/or Xpert MTB/XDR do not detect resistance to fluoroquinolones In both stages, if testing is inconclusive from the first screening sputum specimen, a second sputum can be collected during the screening period. Screening sputum testing details are provided in the Laboratory Manual.
9.3.2 Sputum Assessments for Microbiological Response	One spot sputum specimen at each of these visits may be reserved [redacted]. See Microbiology Laboratory Manual for more details. …	One spot sputum specimen at each of these visits may be reserved [redacted]. See Laboratory Manual for more details. …

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	The trial Microbiology Laboratory Manual specifies the prioritization of sputum tests in the case of limited sputum samples and/or volume. Mycobacterial cultures will be identified by methodologies specified in the Microbiology Laboratory Manual. Results from MGIT liquid culture and solid culture will be combined for the microbiologic component of the primary efficacy end point.	The trial Laboratory Manual specifies the prioritization of sputum tests in the case of limited sputum samples and/or volume. Mycobacterial cultures will be identified by methodologies specified in the Laboratory Manual. Results from MGIT liquid culture and solid culture will be combined for the microbiologic component of the primary efficacy endpoint.
9.3.3 DST	In Stage 1, phenotypic DST will be performed for all drugs in the regimens to maintain the blinding of trial microbiology laboratory staff.	In Stage 1, phenotypic DST will be performed for all regimens to maintain the blinding of trial microbiology laboratory staff.
9.3.4 Mtb Strain Genotyping	Further details will be specified in the Microbiology Laboratory Manual.	Further details will be specified in the Laboratory Manual.
9.3.5 Storage of Sputum Pellets and Mtb Isolates	[redacted]	[redacted]
9.3.6. Sputum Specimen Collection, Preparation, Handling, and Shipping	Specimen collection, preparation, and handling will be performed according to procedures specified in the Microbiology Laboratory Manual. Participants will be educated specifically on how to safely collect sputum specimens at home to minimize risk to others in the home/community. Shipping will be performed according to the Microbiology Laboratory Manual and in compliance with local and international regulations.	Specimen collection, preparation, and handling will be performed according to procedures specified in the Laboratory Manual. Participants will be educated specifically on how to safely collect sputum specimens at home to minimize risk to others in the home/community. Shipping will be performed according to the Laboratory Manual and in compliance with local and international regulations.
9.4.1 CXRs	Post-randomization PA CXRs will be performed at Weeks 4, 9, 17, and 26.	Post-randomization PA CXRs will be performed at Weeks 4, 9, 17, and 26 and Month 12.
9.5.1.1 Initial Screening Visit	• Blood draw for CBC and WBC differential, reticulocyte count, electrolytes, renal function tests, liver enzymes, bilirubin, lactate dehydrogenase, creatine kinase, C-reactive protein (CRP), hemoglobin A1c, hepatitis B surface antigen, hepatitis C antibody, and serum β hCG if FOCBP	• Blood draw for CBC and WBC differential, reticulocyte count, electrolytes, renal function tests, liver enzymes, bilirubin, lactate dehydrogenase, creatine kinase, C-reactive protein (CRP), hemoglobin A1c, hepatitis B surface antigen, hepatitis C antibody, and serum β hCG for pregnancy testing if participant is a FOCBP
9.5.1.2 Baseline Visit	• [redacted] • [redacted]	• [redacted] • Urine collection for point-of-care β hCG for pregnancy testing if participant is a FOCBP [redacted]
9.5.4 Procedures for Participant With Suspected Poor Treatment Response	Investigators may identify a participant with a possible poor treatment response through various methods, including clinical evaluations (eg, new or worsening cough or other TB symptoms), microbiologic results (eg, smear and/or culture reversion to positive after previous conversion to negative), laboratory tests, CXR findings, or a combination of these methods. A possible poor treatment response may be identified while a participant is still taking their trial treatment (ie, treatment failure) or in the follow-up period after completing treatment (ie, post-treatment relapse). In addition to Investigators, the STrAW Concilium can also identify participants with possible poor treatment response and	Investigators may identify a participant with a possible poor treatment response through various methods, including clinical evaluations (eg, new or worsening cough or other TB symptoms), microbiologic results (eg, smear and/or culture reversion to positive after previous conversion to negative), laboratory tests, CXR findings, or a combination of these methods. A possible poor treatment response may be identified while a participant is still taking their trial treatment (ie, treatment failure) or in the follow-up period after completing treatment (ie, post-treatment relapse).

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	communicate their concern to the Investigator (see Section 12.2, STrAW Concilium Charter, and Trial Operations Manual for further details on this interaction between Investigators and the Concilium).	
9.5.6 Post-Early Termination Follow-Up	• [redacted]	
11.2 Statistical Hypotheses	Stage 1 (Phase 2b) In Stage 1, the treatment shortening potential of DBOS and PBOS will be separately assessed in the Per Protocol population by comparing the longitudinal rates of unfavorable outcome status (definition in Section 1.3.3) during treatment of each of DBOS and PBOS relative to that of 2HRZE/4HR. The choice of which experimental regimen (DBOS or PBOS) to consider for study in Stage 2 is not based on strict hypothesis testing, but treatment shortening potential will be declared for a regimen that meets the criteria described below as the co-primary hypotheses. Co-primary hypotheses: • The model-based estimated time point during DBOS treatment that results in a proportion unfavorable outcome status that is equal to the proportion unfavorable outcome status of 2HRZE/4HR at 26 weeks is ≤17 weeks • The model-based estimated time point during PBOS treatment that results in a proportion unfavorable outcome status that is equal to the proportion unfavorable outcome status of 2HRZE/4HR at 26 weeks is ≤17 weeks	Stage 1 (Phase 2b) All Stage 1 analyses will be descriptive; no formal hypothesis testing will be performed. The efficacy analyses will focus on unfavorable outcome status (definition in Section11.3.1) at the end of the treatment period and during treatment of each of DBOS and PBOS relative to that of 2HRZE/4HR. The choice of which experimental regimen (DBOS or PBOS) to consider for study in Stage 2 will be based on a comprehensive review of Stage 1 efficacy and safety results.
11.3 Primary and Key Secondary Endpoints	Stage 1 … Other key secondary efficacy end points include: … • Time to SCC negative for Mtb growth in MGIT during the treatment period for all arms • TTD curves in MGIT for all 3 arms through 8 weeks of treatment as calculated from the area under the TTD vs week curve (AUC) • … • [redacted] • Emergence of resistance to the trial treatment drugs Stage 2 … Other key secondary efficacy end points include:	Stage 1 … Other key secondary efficacy endpoints include: … • Time to SCC to negative for Mtb growth in MGIT during the treatment period for all arms • TTD curves in MGIT for all 3 arms through 4, 8, 9, 13, and 17 weeks of treatment as calculated from the area under the TTD vs week curve (AUC) • … • [redacted] • Emergence of resistance to the trial treatment drugs Stage 2 … Other key secondary efficacy endpoints include:

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	… • Time to SCC in MGIT in each arm; • Trend in TTD in MGIT in each arm through the end of treatment period as calculated from the area under the TTD vs week curve (AUC) • … • [redacted] • Emergence of resistance to the trial treatment drugs	… • Time to SCC in MIGIT in each arm; • Trend in TTD in MGIT in each arm through Weeks 4, 8, 9, 11, 13, 15, and 17 as calculated from the area under the TTD vs week curve (AUC) • … • [redacted] • Emergence of resistance to the trial treatment drugs

11.3.1 Definition of Unfavorable Outcome Status	Unfavorable outcome status will serve as the basis for assessment of the primary efficacy end point in both Stage 1 and Stage 2. Participants that experience one or more of the following events will be categorized as having an unfavorable outcome status (by definition, all participants in the mITT and PP populations have an unfavorable outcome status at baseline):
	• Absence of microbiological cure: defined as having a sputum culture positive for Mtb at the end of treatment according to trial arm or after with a Mtb strain indistinguishable from baseline that is confirmed by a second sample positive for Mtb of the same strain.
	• Death from any cause.
	• Permanent discontinuation of trial treatment before the end of the assigned treatment duration for the following reasons: safety, tolerability, lack of clinical response/treatment failure, participant withdrawal, new requirement for a prohibited concomitant medication, or Investigator judgement. This includes permanent changes of trial treatment to a different TB treatment regimen. It does not include temporary interruptions permitted by the protocol.
	• Extension of TB treatment by the Investigator more than 5 days beyond the end of the assigned treatment duration for any reason
	• Re-start of TB treatment by the Investigator during the post-treatment follow-up period excluding documented TB re-infection with a different Mtb strain than baseline.
	• Positive culture for Mtb at last visit excluding documented TB re-infection with a different Mtb strain than baseline.
	
	In Stage 1, for the primary efficacy end point, unfavorable outcome status will be assessed throughout and at the end of treatment (4 months for DBOS and PBOS arms, 6 months for 2HRZE/4HR arm) to inform the decision to proceed to Stage 2. It should be noted that the unfavorable event criteria of TB treatment restart in the post-treatment follow-up period and positive Mtb culture at last visit in post-treatment follow-up period will not be applicable for the Stage 1 primary
		Unfavorable outcome status will serve as the basis for assessment of the primary efficacy endpoint in both Stage 1 and Stage 2. Participants that experience one or more of the following events following randomization will be categorized as having an unfavorable outcome status:
		• Absence of microbiological cure:
		  ○ Stage 1
		  ▪ DBOS/PBOS: sputum culture positive at Week 17
		  ▪ 2HRZE/4HR: sputum culture positive at Week 17 or at any subsequent time point through Week 26
		  ○ Stage 2
		  ▪ XBOS: sputum culture positive at end of assigned treatment duration
		  ▪ 2HRZE/4HR: sputum culture positive at Week 17 or at any subsequent time point through Week 26
		  ▪ RR/MDR-TB: sputum culture positive at Week 17
		  ○ Positive culture must be with a Mtb strain indistinguishable from baseline.
		• Death from any cause.
		• Permanent discontinuation of trial treatment before the end of the assigned treatment duration for the following reasons: safety, tolerability, lack of clinical response/treatment failure, participant withdrawal, new requirement for a prohibited concomitant medication, or Investigator judgement. This includes permanent changes of trial treatment to a different TB treatment regimen. It does not include temporary interruptions permitted by the protocol.
		• Extension of TB treatment by the Investigator more than 5 days beyond the end of the assigned treatment duration for any reason
		• Re-start of TB treatment by the Investigator during the post-treatment follow-up period excluding documented TB re-infection with a different Mtb strain than baseline.
		• Positive culture for Mtb at last visit excluding documented TB re-infection with a different Mtb strain than baseline.

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	efficacy end point since assessment of the end point stops at the end of the assigned treatment duration.	In Stage 1, for the primary efficacy endpoint, unfavorable outcome status will be assessed throughout and at the end of treatment (4 months for DBOS and PBOS arms, 6 months for 2HRZE/4HR arm) to inform the decision to proceed to Stage 2. It should be noted that the unfavorable event criteria of TB treatment restart in the post-treatment follow-up period and positive Mtb culture at last visit in post-treatment follow-up period will not be applicable for the Stage 1 primary efficacy endpoint, which focuses on unfavorable outcome status through end of treatment for each arm.
11.4 Statistical Methods	Stage 1 (Phase 2b) For each treatment group (DBOS, PBOS, and 2HRZE/4HR), longitudinal rates of unfavorable status during treatment, ie, through Week 17 for DBOS and PBOS and through Week 26 for 2HRZE/4HR, will be modelled using a variation of the MCP-Mod approach (Pinheiro et al, 2014) applied to this case where the "dose" variable is the time course within a subject, assuming the unfavorable status at baseline (Day 1) equals 100% (per the definition of the mITT population, all participants must be confirmed culture positive at baseline) and allowing for a random effect for participant to account for the within-participant correlation of outcome status over time. Based on the model fits, the duration for each of DBOS and PBOS where the unfavorable outcome status rate equals the estimated unfavorable outcome status rate of 2HRZE/4HR at Week 26 will be estimated. Treatment shortening potential (as determined by level of unfavorable outcome status) will be declared if the point estimate of the estimated duration is ≤17 weeks. Additional details of the modelling methodology and variance estimation are described below for Stage 2. The same methodologies will be applied to Stage 1, except that the Stage 1 models are longitudinal and will account for within-participant correlation over time.	Stage 1 (Phase 2b) All Stage 1 analyses will be descriptive; no formal hypothesis testing will be performed. For each treatment group (DBOS, PBOS, and 2HRZE/4HR), the proportion of participants with unfavorable status will be summarized at Week 17 for DBOS and PBOS and Week 26 for 2HRZE/4HR. In addition, unfavorable status will be derived for each participant based on truncated data at earlier milestone time points (e.g., at 2, 2.5, 3, 3.5, 4 months) to create snapshots of unfavorable outcome rates across time for each treatment group. Because unfavorable status has a composite definition, summaries will also show which individual components of the composite outcome were met. The Stage 1 efficacy and safety results will be reviewed comprehensively to inform treatment shortening potential and benefit/risk.
11.5.2 Safety Laboratory Assessments	Summaries by DAIDS toxicity grade (and/or the laboratory normal range) and graded shifts in laboratory values from baseline to each post baseline visits will be also presented.	Summaries by DAIDS toxicity grade (see Section 13.4, Appendix 4) (and/or the laboratory normal range) and graded shifts in laboratory values from baseline to each post baseline visits will be also presented.
11.6 Interim Analyses	An interim analysis will be performed after all Stage 1 participants finish the end of treatment (17 weeks for DBOS and PBOS and 26 weeks for 2HRZE/4HR) to assess the treatment shortening potential of DBOS and PBOS down to at most 4 months' duration. If neither DBOS nor PBOS meet the performance criteria, the trial will stop and neither regimen will advance to Stage 2. If only one of the DBOS or PBOS regimens meets the performance criteria, that regimen will be considered for progression to Stage 2. If both DBOS and PBOS meet the performance criteria, the regimen that will be considered for proceeding to Stage 2 will be the regimen with the more favorable profile overall as adjudicated by collective deliberation of the partner organizations supporting the conduct of the trial, including, but not limited to, assessment of safety (comparison of rates of SAEs and severe AEs, etc.), tolerability, pharmacokinetics, and alignment with the target regimen profile as outlined in Section 2.1.	An interim analysis will be performed after all Stage 1 participants finish the end of treatment (17 weeks for DBOS and PBOS and 26 weeks for 2HRZE/4HR) to assess the treatment shortening potential of DBOS and PBOS down to at most 4 months' duration. If neither DBOS nor PBOS shows evidence of treatment shortening potential with an acceptable safety profile, the trial will stop and neither regimen will advance to Stage 2. If only one of the DBOS or PBOS regimens shows evidence of treatment shortening potential with an acceptable safety profile, that regimen will be considered for progression to Stage 2. If both DBOS and PBOS show evidence of treatment shortening potential with acceptable safety profiles, the regimen that will be considered for proceeding to Stage 2 will be the regimen with the more favorable profile overall as adjudicated by collective deliberation of the partner organizations supporting the conduct of the trial, including, but not limited to, assessment of safety

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	Continuous monitoring for futility by the IDMC based on the 12-months post-randomization unfavorable outcome rate end point will be implemented in both Stage 1 and Stage 2, after at least 20 participants have been enrolled in each group.	(comparison of rates of SAEs and severe AEs, etc.), tolerability, pharmacokinetics, and alignment with the target regimen profile as outlined in Section 2.1. Regular monitoring for futility by the IDMC based on the 12-months post-randomization unfavorable outcome rate endpoint will be implemented in both Stage 1 and Stage 2, after at least 20 participants have been enrolled in each group.
11.7 Sample Size Justification	Number of Participants Stage 1 (N=129) In Stage 1, approximately 43 participants per arm will be enrolled in a 1:1:1 randomization ratio to the treatment groups described in Figure 1. It is anticipated that a small number (≤10%) of enrolled participants will be confirmed with pre-treatment baseline sputum culture results negative for growth of drug-susceptible (defined as susceptible to both isoniazid and rifampicin) Mtb. After excluding these participants from the primary analysis and accounting for participants potentially withdrawing early from the trial, each arm is expected to include approximately 40 participants in the modified-intent-to-treat (mITT) population for analysis.	Number of Participants Stage 1 (N=129) In Stage 1, approximately 43 participants per arm will be enrolled in a 1:1:1 randomization ratio to the treatment groups described in Figure 1.
11.7 Sample Size Justification	Stage 1 (Phase 2b) Simulations The operating characteristics of the Stage 1 decision criteria were examined via clinical trial simulation. Five underlying true response profiles of XBOS were examined relative to 2HRZE/4HR as shown in Figure 4. In addition, 3 sample sizes (N=30, 40 and 50/group) and 3 sampling strategies (12, 15, or 25 samples collected for each participant) were examined. Figure 4 True Underlying Response Profiles Examined Via Clinical Trial Simulation	Stage 1 (Phase 2b) Simulations The operating characteristics of the Stage 1 primary endpoint (unfavorable outcome rate at end of treatment) were examined via simulation under binomial distributions with n=43 per treatment group and true unfavorable outcome probabilities as shown in the first and second columns of Table 13. The third column shows, under assumed exponential distributions, the calculated week at which the XBOS unfavorable outcome probability is equal to that of 2HRZE/4HR. For example, if the true unfavorable outcome probability is 0.1 for 2HRZE/4HR at 26 weeks and 0.05 at 17 weeks for XBOS, then XBOS has an unfavorable outcome probability of 0.1 at 13.1 weeks. Based on simulated data, the final column of Table 13 shows the estimated probability of observing an XBOS unfavorable outcome rate at 17 weeks that is no greater than that of 2HRZE/4HR at 26 weeks. Specifically, with 43 participants per arm, the estimated probability of observing same or improved unfavorable outcome rate with 17 weeks of XBOS relative to 26 weeks of 2HRZE/4HR is 56-58% when the underlying probabilities are equal; 75-87% when the unfavorable outcome probability for XBOS is 5 percentage points lower than 2HRZE/4HR; and above 89% when the unfavorable outcome probability for XBOS is 10 percentage points lower than 2HRZE/4HR. It is expected that <10% of participants could have pre-treatment baseline sputum culture results negative for growth of drug-susceptible (defined as susceptible to both isoniazid and rifampicin) Mtb. Accounting for exclusion of these participants from

<table>
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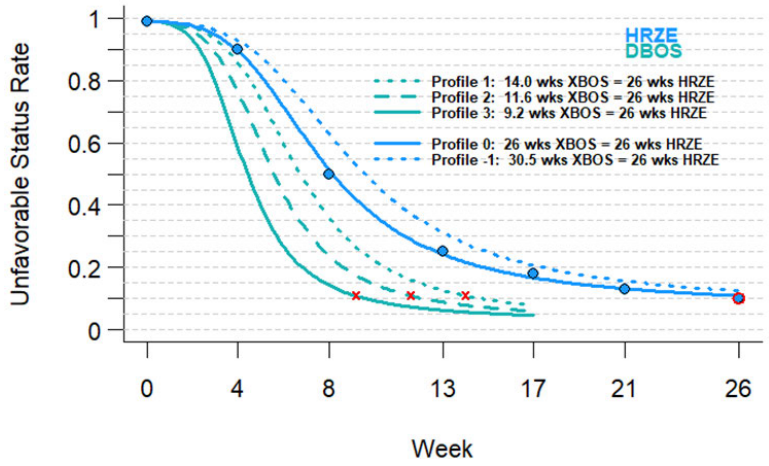

Figure 5 shows the probability of estimating a duration of ≤17 weeks, where the failure rate equals the 26-week 2HRZE/4HR failure rate for each of the underlying true response profiles (columns) versus the number of participants and number of samples collected for each participant (rows). Specifically, with 40 participants per arm and 15 longitudinal assessments per participant, there is <10% probability of concluding treatment shortening potential when XBOS is worse than 2HRZE/4HR; there is ~20% probability of concluding treatment shortening potential when XBOS equals 2HRZE/4HR; there is ~85% probability of concluding treatment shortening potential when 11.6 weeks of XBOS equals 2HRZE/4HR (Profile 2); and there is ~90% probability of concluding treatment shortening potential when 9.3 weeks of XBOS equals 2HRZE/4HR (Profile 3).

Figure 5 Probability of Duration Estimation</td><td>
the mITT population, the operating characteristics with n=40 per treatment group are similar to those summarized above.

Table 13 Operating Characteristics of Unfavorable Outcome at End of Treatment

<table>
<tr><th colspan="4">Unfavorable outcome probability with n=43 per treatment group</th></tr>
<tr><th>True 2HRZE/4HR at 26 weeks</th><th>True XBOS at 17 weeks</th><th>Calculated week when XBOS = 26-week 2HRZE/4HR [a]</th><th>Estimated probability that XBOS at 17 weeks ≤ 2HRZE/4HR at 26 weeks[b]</th></tr>
<tr><td>0.10</td><td>0.10</td><td>17.0</td><td>0.58</td></tr>
<tr><td></td><td>0.05</td><td>13.1</td><td>0.87</td></tr>
<tr><td>0.15</td><td>0.15</td><td>17.0</td><td>0.57</td></tr>
<tr><td></td><td>0.10</td><td>14.0</td><td>0.81</td></tr>
<tr><td></td><td>0.05</td><td>10.8</td><td>0.97</td></tr>
<tr><td>0.20</td><td>0.20</td><td>17.0</td><td>0.56</td></tr>
<tr><td></td><td>0.15</td><td>14.8</td><td>0.75</td></tr>
<tr><td></td><td>0.10</td><td>12.7</td><td>0.89</td></tr>
<tr><td colspan="4">a. Based on exponential distribution
b. Proportion of 5000 binomial paired simulations for which the number of XBOS participants with unfavorable outcome is <= the number of 2HRZE/4HR participants with unfavorable outcome (PASS 2022)</td></tr>
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	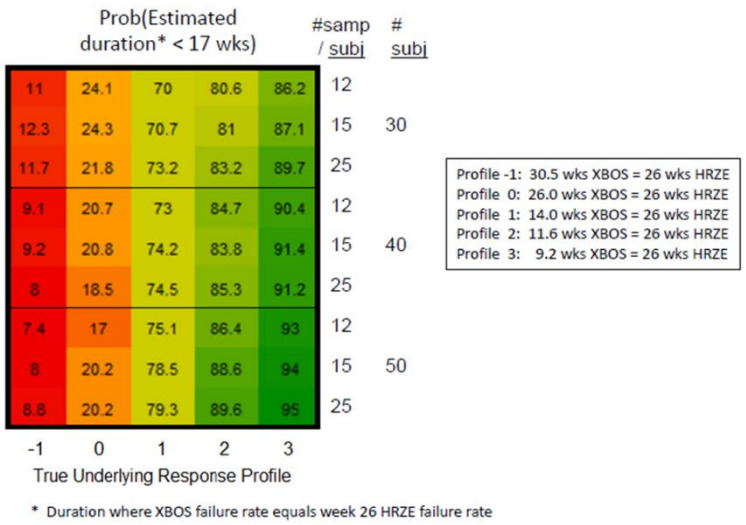	
12.2 STrAW Concilium	A STrAW Concilium will be established for the trial for the following purposes: • Monitor individual trial participants' response to treatment through the review of standardized STrAW reports produced at important time points • Provide expert clinical consultation to Investigators on challenging clinical scenarios, including all participants where the Investigator wants to permanently stop one or more trial medications, continue trial treatment past the assigned duration, or restart TB treatment after the completion of trial treatment (see Section 8.3.2 and Section 9.5.4). The STrAW Concilium will be composed of experts in TB clinical management and microbiology. The Concilium will operate according to a charter detailing its structure, participants, and procedures. Concilium members will not be blinded to trial regimen assignment.	See Section 1.6 for description of the STrAW Concilium.
13.2.5 Informed Consent Process	An impartial witness is defined as a person who is independent of the trial, cannot be unfairly influenced by trial team members, attends the informed consent process if the participant or their legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. National and local regulations regarding the informed consent process will be followed.	An impartial witness is defined as a person who is independent of the trial, cannot be unfairly influenced by trial team members, attends the informed consent process if the participant cannot read, and who reads the informed consent form and any other written information supplied to the subject. National and local regulations regarding the informed consent process will be followed.

Section Number	Text in Version 1	Text in Version 2 (Amendment 1)
	Participants must be informed that their participation is voluntary. The Investigator or designee will explain the trial to the participant or his/her legally authorized representative and answer all questions regarding the trial.	Participants must be informed that their participation is voluntary. The Investigator or designee will explain the trial to the participant and answer all questions regarding the trial.
Multiple sections	"end point" or "end points"	"endpoint" or "endpoints"

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Signature Page for: Gates MRI-TBD06-201 Protocol Version 3.0 (06 Feb 2024)

Gateway RIM Document #: TBD06-CLIN-000017 v4.0

Document Approvals	
eSignature Approval	[redacted] Chief Medical Officer 06-Feb-2024 18:22:01 GMT+0000
eSignature Approval	[redacted] Clinical Development 06-Feb-2024 18:51:55 GMT+0000
eSignature Approval	[redacted] Biometrics & Data Management 06-Feb-2024 19:03:27 GMT+0000