A Phase IIc, Open-Label, Randomized Controlled Trial of Ultra-Short Course Bedaquiline, Clofazimine, Pyrazinamide and Delamanid versus Standard Therapy for Drug-Susceptible Tuberculosis (PRESCIENT)

DMID protocol 22-0018

Acronym: "PRESCIENT" (Parabolic Response Surface Derived Regimen for Treatment Shortening in TB)

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Brigham and Women's Hospital

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(This is PRESCIENT protocol Version 5.0 with personal identifiable information redacted)

STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Participants), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, Report of the National Commission for the Protection of Human Participants of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Participants, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- South African Good Clinical Practice: Clinical Trial Guidelines (2019)

SIGNATURE PAGE

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of participants.

Site Investigator Signature:

Signed: _____ Date: _____

Name
Title

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LIST OF ABBREVIATIONS

AE	Adverse Event
AFB	Acid Fast Bacilli
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
BCZD	Bedaquiline/Clofazimine/Pyrazinamide/Delamanid
BDQ	Bedaquiline
CFR	Code of Federal Regulations
CFZ	Clofazimine
CFU	Colony Forming Unit
CI	Confidence Interval
CRF	Case Report Form
CXR	Chest X-Ray
DLM	Delamanid
DOT	Directly Observed Therapy
DS-TB	Drug Susceptible Tuberculosis
DST	Drug Susceptibility Testing
DSMB	Data and Safety Monitoring Board
EBA	Early Bactericidal Activity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMB	Ethambutol
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
INH	Isoniazid
IRB	Institutional Review Board
LFT	Liver Function Test
LPA	Line Probe Assay
MDR-TB	Multidrug-Resistant Tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MIC	Minimum Inhibitory Concentrations
MOP	Manual of Procedures
ms	Milliseconds
Mtb	*Mycobacterium tuberculosis*
NIH	National Institutes of Health

NTP	National Tuberculosis Program
OHRP	Office for Human Research Protections
PD	Pharmacodynamic
PI	Principal Investigator
PID	Participant identification number
PK	Pharmacokinetics
PRS	Parabolic Response Surface
PTB	Pulmonary tuberculosis
PZA	Pyrazinamide
QA	Quality Assurance
QC	Quality Control
QTc	Corrected QT Interval
QTcF	Corrected QT interval based on the Fridericia correction
RH	Rifampicin/Isoniazid
RHZE	Rifampicin/Isoniazid/Pyrazinamide/Ethambutol
RIF	Rifampicin
RPT	Rifapentine
RMST	Restricted Mean Survival Time
SAE	Serious Adverse Event
SOC	Standard of Care
SOP	Standard Operating Procedure
TB	Tuberculosis
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis

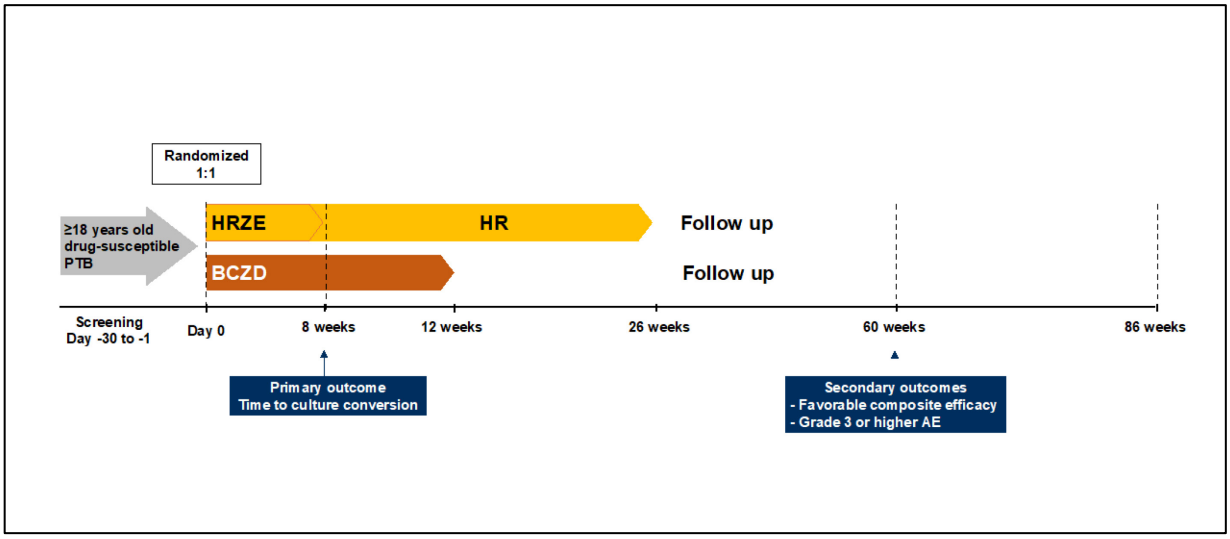
PROTOCOL SUMMARY

Title	A phase IIc, open-label, randomized controlled trial of ultra-short course bedaquiline, clofazimine, pyrazinamide and delamanid versus standard therapy for drug-susceptible tuberculosis.
Acronym	PRESCIENT
Study Design	Phase IIc, open-label, multi-center, randomized controlled trial to evaluate the microbiological efficacy of a rifamycin-free ultra-short regimen for DS-TB. Eligible participants will be randomized in a 1:1 ratio to the experimental drug combination bedaquiline, clofazimine, pyrazinamide and delamanid (BCZD) or standard anti-TB therapy. Randomization will be stratified by presence of lung cavitation and HIV status.
Study Phase	IIc
Study Population	The trial will enroll 156 adults (≥18 years of age) with confirmed smear-positive drug-susceptible pulmonary TB prior to receipt of >5 days of treatment for the index episode, regardless of HIV status. Patients with HIV are eligible if they have CD4 counts ≥200 cells/mm^3, if they are receiving ART or plan to initiate ART within 8 weeks after enrollment. The trial will enroll participants in Port-au-Prince, Haiti, and Cape Town, South Africa. There will be no exclusion on the basis of sex/gender, racial or ethnic group.
Number of Sites	2 (GHESKIO, Haiti and University of Cape Town, South Africa)
Description of Study Intervention	Participants will be randomized to Arm 1 or 2: • Arm 1 (Experimental): BDQ 200 mg for 12 weeks + PZA 1000 - 2000 mg (according to weight) for 12 weeks + CFZ 300 mg for 2 weeks, followed by 100 mg for 10 weeks + DLM 200 mg for 12 weeks, all given once daily. • Arm 2 (Standard of Care): RIF, INH, EMB and PZA for 8 weeks, followed by RIF and INH for 18 weeks; given daily in fixed dose combinations at standard weight-based doses.

Study Objectives	Primary To compare time to liquid culture conversion through 8 weeks for BCZD vs. standard treatment in HIV-positive and -negative adults with DS-TB. Secondary • To compare safety (adverse events) and tolerability over 60 weeks. • To compare cumulative probability of experiencing favorable composite outcome at 60 weeks between participants treated with BCZD versus with standard treatment. • To detect treatment-emergent resistance with BCZD. • To compare time to liquid culture conversion through 12 weeks for BCZD vs. standard treatment • To compare time (days) to positivity in liquid culture over 8 weeks Exploratory • To compare cumulative probability of experiencing favorable composite outcome (defined in section 9.2) at 86 weeks between participants treated with BCZD vs. with standard treatment • To explore the effect of drug exposure, derived from population PK models based on observed concentrations, on time to culture positivity as a pharmacodynamic measure of mycobacterial burden and treatment response, and on QT prolongation. • To compare post-tuberculosis pulmonary sequelae between BCZD vs. standard group participants with the use of spirometry, chest radiographs, respiratory and quality of life questionnaires, and biomarkers. • To assess the association between food insecurity and time to culture conversion and probability of experiencing a favorable composite outcome at 86 weeks in both groups. • To collect blood (and its derivatives), sputum, and oral swabs for potential future use in diagnostic, biomarker, or PK analyses.

Duration of Individual Participant Participation	86 weeks
Estimated Time to Last Participant/Last Study Day	September 2023 – January 2027

Figure 1. Schematic of Study Design



KEY ROLES

(Information redacted)

Contact Principal Investigator	
Principal Investigator	
Site PI, UCT	
Site PI, GHESKIO	
Statistician	
Statistical and Data Analysis Center	

1 BACKGROUND AND SCIENTIFIC RATIONALE

1.1 Background

1.1.1 Need for shorter therapy in DS-TB

Globally, tuberculosis (TB) remains the leading cause of death from a single infectious agent.[1] Standard first-line therapy for TB is effective (~85% cure in programmatic settings) but is complicated by long treatment duration, poor tolerability, and drug-drug interactions with rifamycins, especially with antiretroviral agents.[2-5] In addition, the global prevalence of isoniazid monoresistance is estimated at about 8% of all new cases, and use of RHZE leads to worse outcomes when treating isoniazid mono-resistant strains than when treating fully susceptible strains.[6] These treatment limitations have important implications for global TB control and threaten attainment of the World Health Organization (WHO) End TB goals. A well-tolerated and efficacious rifamycin-free regimen that can shorten TB treatment duration is needed.

Several Phase II/III trials of dose-optimized rifamycin-based and novel rifamycin-free regimens for DS-TB are underway, at treatment durations ranging from 12 to 17 weeks. Conventional approaches to selecting potential regimens for treatment-shortening involve adding or substituting drugs to the existing rifamycin-based regimen based on individual performance in preclinical models and Phase II trials. This strategy has been largely unsuccessful, unable to yield shorter regimens that translate into similar clinical outcomes to standard 6-month therapy.[7-9] A notable exception is TBTC Study 31/A5349, for the first time demonstrating non-inferiority of a 4-month regimen for pulmonary DS-TB.[9] Selection of the successful S31 regimen, which includes optimized rifapentine plus moxifloxacin, was based on extensive pharmacokinetic (PK) data and performance in mouse infection models. S31 represents a milestone in DS-TB regimen development, confirming the ability of mouse and PK models to predict effective TB regimens in patients. However, the successful S31 regimen has important limitations, including ongoing reliance on a rifamycin and requiring 4 months of therapy, still a substantial treatment commitment. Even shorter regimens are needed that incorporate potent newly developed drugs and that have a high probability of successful translation from pre-clinical evaluations.

1.1.2 Pre-Clinical Data in Support of the Proposed Experimental Regimen

Synergies and antagonisms among drugs used in combination greatly influence their capacity to kill mycobacteria *in vitro* and *in vivo* as well as their optimal doses for safety and efficacy, but have not been a major consideration in the development of experimental regimens.[10-13] A strategy for selecting treatment shortening regimens that accounts for individual drug potency and safety profiles observed from early phase trials, plus the presence of synergy when used in combination, could increase the probability of regimen success.

The study team has pioneered use of an artificial-intelligence-enabled parabolic response surface (PRS) platform in conjunction with an *in vitro Mycobacterium tuberculosis (*Mtb*)*-infected macrophage cell culture assay amenable to high-throughput screening to evaluate

synergy among the huge number of possible drug-dose combinations.[10-13] This strategy allows rapid identification of the most effective drug-dose combinations and allows optimization of the *in vivo* doses of each drug in a regimen for definitive testing of efficacy in lung sterilization and achieving relapse-free cure in a mouse model of pulmonary TB.[11-13] Using these methods, Horwitz (co-investigator) identified several PRS regimens that are dramatically more effective than the standard WHO-recommended DS-TB treatment regimen (RHZE), achieving relapse-free cure in the conventional BALB/c mouse model in as little as 3 or 4 weeks vs. 16-20 weeks for the standard regimen (see Tables 1 and 2, and Figure 2).[11-13]

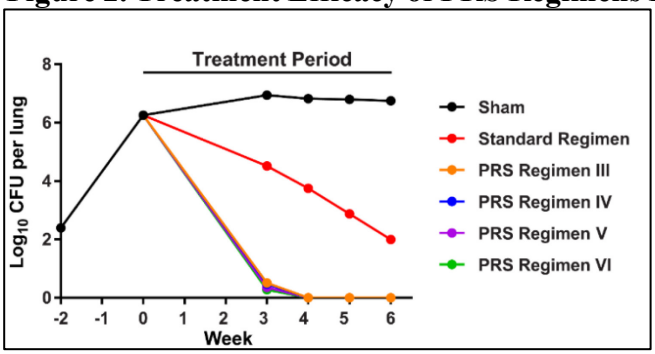
This is substantially shorter than time to relapse-free cure in murine studies supporting the successful S31 trial, and the ongoing A5362 trial, in which CFZ and rifapentine achieved cure at 10 to 12 weeks.[14-16] Furthermore, BDQ, CFZ, PZA, and SQ109 (PRS regimen III) was tested in C3HeB/FeJ (Kramnik) mice, which, in contrast to BALB/c mice, develop massive caseating necrotic granulomas; the lungs of PRS Regimen III-treated mice were rapidly sterilized and the mice achieved relapse-free cure just as fast as in BALB/c mice (see Figures 3 and 4).[13] The most effective PRS drug combinations included BDQ, CFZ, and PZA at optimal dose ratios, achieving 100% relapse-free cure in BALB/c mice within 3 weeks, indicating bactericidal and sterilizing ability; in contrast, in the same experiment, 100% of mice treated with the standard regimen for 6 weeks relapsed (i.e. 0% relapse-free cure).[13] Adding DLM as a 4th drug was equivalent in potency to this successful 3-drug regimen (BDQ-CFZ-PZA).[13] See Tables 1 and 2, and Figure 2.

Table 1. Overall Efficacy of BCZD vs. Standard Regimen in Murine Model

	Standard Regimen[a]	**BDQ-CFZ-PZA+/- DLM[b]**
EBA-14 days (EBA_{14})[c]	0.14 Log_{10} CFU Reduction/Day	0.36 or 0.37 Log_{10} CFU Reduction/Day
Time to 100% Lung Sterilization[d]	16 weeks	5 weeks
Time to 100% Relapse-free Cure[e]	20 weeks	3 weeks

[a] Standard Regimen (mg/kg): INH(25)/RIF(10)/EMB(100)/PZA(150) x 8 weeks; then INH(25)/RIF(10)
[b] PRS Regimen V (mg/kg): CFZ (25)/BDQ (40)/PZA(185)/DLM (0.83)
[c] BALB/c mice were infected by aerosol with Mtb Erdman strain, and starting 2 weeks later (Total lung CFU=6.75 Log10) treated daily by gavage for 14 days with the standard or experimental regimen; euthanized; and total lung CFU assayed (n=5/group). Data are the mean log10 CFU of Mtb reduction per day over 14 days of treatment.[13]
[d] In comparable experiments, BALB/c mice were infected by aerosol with Mtb Erdman strain, and starting 2 weeks later treated by gavage (5 days/week) with the standard or experimental regimen; euthanized at 3, 4, 5, or 6 weeks (experimental regimen) or at 8, 12, 16 or 20 weeks (standard regimen) (n=5/group/time point); and the entire lung cultured for Mtb. Data are the first time point at which 100% of mice had 0 CFU in their entire lung.[12,13]
[e] In comparable experiments, BALB/c mice were infected by aerosol with Mtb Erdman strain, and starting 2 weeks later, treated by gavage (5 days/week) for 3, 4, 5, or 6 weeks (experimental regimen) or 8, 12, 16 or 20 weeks (standard regimen) (n=10/group/time point); rested for 3 months; euthanized; and the entire lung cultured for Mtb. Data are the first time point at which 100% of mice had 0 CFU in their entire lung.[12,13]

Figure 2. Treatment Efficacy of PRS Regimens III-VI vs. Standard in BALB/c Mice[13]



PRS Regimen III = CFZ/BDQ/PZA/SQ109

PRS Regimen IV = CFZ/BDQ/PZA/AC

PRS Regimen V = CFZ/BDQ/PZA/DLM

PRS Regimen VI = CFZ/BDQ/PZA

Table 2. BCZD and BCZ vs. Standard Regimen: Assessment of Relapse-free Cure Three Months after Treatment Cessation in BALB/c Mice[13]

Treatment Duration (week)	Standard Regimen	BCZD	BCZ
3	—	0/10 (0%)	0/10 (0%)
4	—	0/10 (0%)	0/10 (0%)
5	—	0/10 (0%)	0/10 (0%)
6	10/10 (100%)	0/7 (0%)	0/10 (0%)

Figure 3. BCZ + SQ109 (PRS Regimen III) vs. Standard Regimen: Assessment of Relapse-Free Cure Three Months after Treatment Cessation in C3HeB/FeJ (Kramnik) Mice

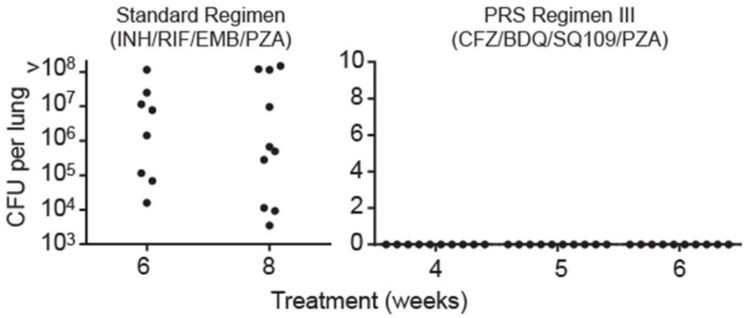
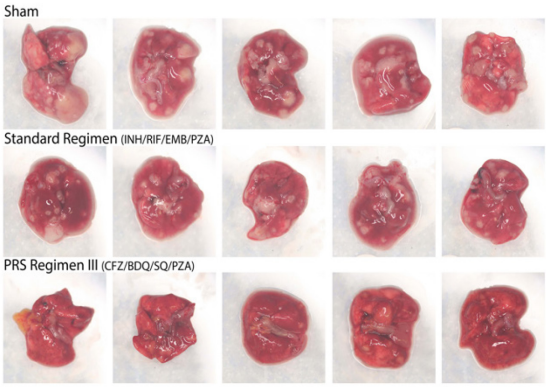


Figure 4. Lung Gross Pathology in C3HeB/FeJ Mice upon Completion of Four Weeks of Treatment



1.2 Scientific Rationale

1.2.1 Regimen Selection: Efficacy Considerations for Individual Drugs

Individual drugs in the BCZD regimen have demonstrated bactericidal activity alone and in combination, with well-documented additive effects. BDQ has potent dose-dependent bactericidal activity on its own, and in combination with CFZ and PZA in pre-clinical studies and patients.[17-21] BDQ-containing combinations exert potent antimicrobial activity beyond the 14 initial days of treatment, which translates into treatment shortening in clinical studies.[18] Similar observations have been made with CFZ, which alone does not have measurable early bactericidal activity (EBA) in mouse models or patients, but contributes potent sterilizing effects and treatment shortening potential when added to other anti-TB drugs for both DS- and DR-TB, with data from clinical trials and observational studies in support of its efficacy.[15,22-25] The relative delay or even absence of EBA therefore does not predict antituberculosis activity later in treatment. PZA has detectable EBA in humans, significant dose-dependent EBA in BALB/c and Kramnik mouse models when used alone and has well-established treatment shortening ability.[16,21,26] Importantly, the combination of PZA and BDQ has additive bactericidal activity and is synergistic for sterilization in mouse models, including in Kramnik mice.[16,19,27,28] DLM also contributes significant EBA on its own.[29,30]

Individual drugs in the regimen penetrate pulmonary TB lesions to varying extents. Although BDQ preferentially accumulates in the cellular rim of TB granulomas in the Kramnik mouse model, it also penetrates caseum, including central caseum, at concentrations above wild-type minimum inhibitory concentration (MIC).[16] Despite a concentration gradient, BDQ appears to achieve therapeutic exposures across the entire lesion in mouse and rabbit lungs (V. Dartois, personal communication).[16] In contrast, CFZ does not diffuse into necrotic foci of TB lesions.[31] However, the drug accumulates in cellular tissues at high concentrations relative to plasma, including cavity wall, outer cellular layers of granulomas, and fibrotic lesions, predicted to translate into exposures above the MIC for the entire dosing interval.[31,32] In mice, both PZA and its active metabolite, pyrazinoic acid, partition homogenously across lung tissue, cellular lesions, and caseous necrotic granulomas.[16,33] DLM has a large volume of distribution, including into central caseum (V. Dartois, personal communication). Synergistic mechanisms of action, different target subpopulations of metabolically distinct bacteria, and non-overlapping penetration characteristics likely contribute to observed efficacy of BCZD when used in combination. The BCZD regimen was identified using an unbiased PRS approach, but the bactericidal and sterilizing ability confirmed in other experiments and settings, and favorable intra-lesional PK, provides strong additional justification for evaluation as a treatment shortening regimen.

1.2.2 Mitigating Risk of Resistance with a Four-Drug Regimen

Though the BDQ-CFZ-PZA core was as potent as 4-drug combinations in murine experiments, the potential for emergent resistance may undermine the effectiveness of a 3-drug regimen when used in programmatic settings. Background resistance to core agents

in the BCZD regimen is uncommon for patients with DS-TB, and for all except PZA in DR-TB. Reported prevalence of BDQ resistance-associated variants (RAVs) or elevated MIC among pretreatment rifampicin-resistant *Mtb* isolates in TB programs ranges from 4 - 8%.[34-37] Resistance to CFZ without prior exposure has also been reported, although this was rare in a South African DR-TB cohort study, with MICs above the critical concentration detected in only 1.2% (2/154) (Wasserman, Warren; unpublished).[37,38] Data on BDQ and CFZ resistance in clinical rifampicin-susceptible *Mtb* isolates is scarce, but is likely a rare occurrence.[34] Similarly, prevalence of PZA resistance is low in DS-TB. No cases of phenotypic PZA resistance were detected in a South African study that tested 80 unique DS-TB isolates,[39] and only 1.4% (75/5511) of incident DS-TB cases in New York were resistant to PZA.[40,41] In a meta-analysis based on 8 studies, the median prevalence of PZA resistance in culture isolates of *Mtb* that were susceptible to both INH and RIF was 5%.[42]

An additional risk is the potential for shared resistance between BDQ and CFZ. Reduced susceptibility to both drugs due to de-repression of the *MmpS5-MmpL5* efflux pump (non-target based mutations in *Rv0678*) or loss-of-function mutations in *pepQ* (encoding a cytoplasmic proline-specific aminopeptidase) have been demonstrated in mouse models, and there is evidence of emergent BDQ resistance in DR-TB programs with increasing use.[35,36,38,43,44] To mitigate the risk of regimen failure as a result of pre-existing resistance and shared resistance mechanisms, and to enhance durability, we have selected a 4-drug experimental regimen, adding DLM to the BDQ-CFZ-PZA core. DLM received regulatory approval after demonstrating benefit, including survival, as add-on therapy in DR-TB in clinical studies.[30,45] Although it had no effect on culture conversion in a Phase III trial, use of DLM was associated with a reduction in fluoroquinolone resistance and did not lead to excess adverse events (including severe QT prolongation).[46] Baseline DLM resistance among trial participants with DR-TB was rare (< 1%, n = 657).[47] Because of its excellent safety record and few drug-drug interactions, DLM remains an appealing option as part of combination therapy in novel treatment regimens, as well as for TB prevention, and is undergoing clinical evaluation for these indications.[48,49] These characteristics support inclusion of DLM in an experimental regimen for DS-TB, primarily to protect against emergence of drug resistance.[19,21,50]

Concerns have been raised about use of current second-line drugs in DS-TB regimens.[51] However, unlike standard RHZE therapy, which is now compromised by substantial isoniazid resistance, there has not yet been prolonged and widespread use of experimental agents used in BCZD. Regimens containing new drugs with low rates of pre-existing resistance and in optimized fixed combinations will likely help preserve clinical utility, possibly beyond the lifespan of RHZE.[52] To quantify risk and inform further clinical development, we shall measure and report occurrence of treatment-emergent resistance in our trial.

1.2.3 Dose Selection in the Experimental Regimen

Optimized dosing of experimental agents in this trial is based on successful murine experiments plus clinical PK data. We shall provide BDQ 200 mg for 12 weeks, PZA 1000

- 2000 mg (according to weight) for 12 weeks, CFZ 300 mg for 2 weeks, followed by 100 mg for 10 weeks, and DLM 200 mg for 12 weeks, all given orally once daily (see Table 4). BDQ 200 mg/day achieves comparable exposures to standard dosing (400 mg loading dose for 2 weeks followed by 200 mg 3x/week) and, due to the long elimination half-life, is expected to remain above the BDQ wild-type MIC well beyond the 12-week treatment duration. This dosing regimen was not associated with excess adverse events and showed superior efficacy compared with standard dosing in a Phase IIb trial for DS-TB (NC-005).[53] Omission of the lead-in dose plus daily dosing will support adherence.

The optimal dose for CFZ in TB treatment is unknown. Simulations based on PK data from DR-TB patients in South Africa showed that CFZ 300 mg daily for 2 weeks followed by 100 mg daily is predicted to achieve earlier time to concentration above a putative efficacy target (0.25 mg/L – wild-type MIC value) than standard dosing (100 mg daily).[54] Modeling also showed that elimination half-life after repeated dosing is ~30 days, with measurable concentrations expected beyond 8 weeks, potentially providing ongoing efficacy. This dosing regimen is predicted to result in QTcF > 450 ms in 3.2% vs. 2.6% and no significant difference in ΔQTcF at 8 weeks compared with standard dosing, strongly supporting safety.[55] This is the same dose of CFZ that is being used in the ongoing A5362 (CLOFAST) trial.

PZA dosing is based on a probability of target attainment analysis in an African population.[56] Participants in WHO weight bands I (30 - 37kg) and II (38 - 54kg) will be provided higher doses to account for increased clearance with allometric scaling. This dosing regimen is aligned to optimized dosing identified through PRS analysis; will provide more equitable exposures across weight bands; and support simplified administration.

The approved dose of DLM for DR-TB is 100 mg twice daily. To reduce pill burden for a DS-TB regimen, we shall provide 200 mg daily dosing for DLM. Exposures with 200 mg daily dosing far exceed the suggested critical concentration (0.2 µg/ml) for the dosing interval.[49,57] Multiple once-daily doses of 200 mg were well-tolerated and not associated with clinically significant QT changes in a healthy volunteer study; DLM 200 mg daily was safely used for 4 months of therapy in the phase 3 Trial 213.[46,49] The ideal dose identified by the PRS approach was 0.83 mg/kg (lowest dose) in mice, which is considered equivalent to ~50 mg/day in humans; the difference between this dose and the highest dose studied (9x more) was negligible in terms of efficacy. Since the major role of DLM is to protect against the emergence of drug resistance, the higher dose is selected.

1.3 Purpose of the Study

Given the translational ability of murine models and based on the above preclinical evidence, we hypothesize that BCZD will demonstrate superior microbiologic efficacy relative to standard therapy (RHZE) during the first 12 weeks of treatment for patients with DS-TB. To test this, we shall conduct a Phase IIc randomized controlled trial to investigate the efficacy and safety of a 12-week regimen of BCZD, paving the way for a definitive treatment-shortening trial. Clinical benefits of BCZD include potential for ultrashort

therapy, activity against INH-resistant infections, and avoidance of the drug-drug interactions with rifamycins, particularly in combination with ART. Constituent medications are all generally well tolerated with excellent safety profiles. Importantly, all drugs are registered and accessible for the trial (as well as for treatment in TB programs). This experimental regimen is not being evaluated in current and recently-completed treatment-shortening studies of DS-TB, most of which include rifamycins, with longer treatment durations than our study (see Table 3). The PRESCIENT trial will thus provide rapid and high-quality clinical evidence for an ultrashort DS-TB regimen, informing development of other mechanistic approaches to TB regimen selection and the progression to definitive trials.

Table 3. Current or Recently-completed IIb/III Treatment Shortening Trials for DS-TB

Trial Name	Drug/Regimen *	Duration	Phase	N	Site	Clinicaltrials.gov
APT Study	Pa, H, RIF, Z Pa, H, RBT, Z	3 months	2b	183	South Africa	NCT02256696
TRUNCATE-TB	RIF, H, Z, E, LZD RIF, H, Z, E, CFZ RPT, H, Z, LFX, LZD H, Z, E, BDQ, LZD	2 months	2 /3	900	4 countries	NCT03474198
SimpliciTB	BDQ, Pa, MFX, Z	4 months	2c	455	10 countries	NCT03338621
CLO-FAST (A5362)	RPT, CFZ, Z, H, E	3 months	2c	185	8 countries	NCT04311502
RIFASHORT	RIF 1200/1800, H, Z, E	4 months	3	654	6 countries	NCT02581527

* Pa,pretomanid; H, isoniazid; RIF, rifampicin; Z, pyrazinamide; RBT, rifabutin; E, ethambutol; LZD, linezolid; CFZ, clofazimine; LFZ, levofloxacin; BDQ, bedaquiline; MFX, moxifloxacin; RPT, rifapentine

1.3.1 Study Population

The study will enroll men and women with smear-positive, DS-TB who are at least 18 years of age, with or without HIV co-infection. No participant will be excluded based on sex/gender, racial or ethnic group. Women will be recruited in the same manner as men. We anticipate that approximately 40% of the enrolled participants will be female. The reason for the slightly lower anticipated enrolment rate for females is the higher incidence of TB in males. There is no maximum age for participation.

The study will enroll participants in Port au Prince, Haiti and Khayelitsha, South Africa. The trial sites are appropriate given the high incidence of TB in these countries. In 2019, Haiti had an estimated TB incidence of 170/100,000 (16% known to be HIV-positive), according to the WHO.[58] In the same year, South Africa had an estimated TB incidence of 615/100,000 (58% known to be HIV-positive).[58]

The study population will be drawn from patients who present with TB symptoms in the outpatient setting. The study will not enroll pregnant women, children, or prisoners. Pregnant and breastfeeding women are excluded because safety of the experimental regimen on the fetus is unknown and because of altered pharmacokinetics in pregnancy. Children who are under 18 years of age will be excluded because TB treatment guidelines and dosing vary between adults and children.

1.4 Potential Risks and Benefits

1.4.1 Potential Risks

Risks associated with study participation include the possibilities that the experimental regimen will have efficacy that is inferior to the standard regimen and/or the experimental regimen will be more toxic than the standard regimen, confidentiality risks, social harm of a new HIV diagnosis, and complications from study procedures.

As described above, the experimental regimen (BCZD) is more effective than the standard WHO-recommended DS-TB treatment regimen (RHZE) in murine models, achieving relapse-free cure in the conventional BALB/c mouse model in as little as 3 or 4 weeks vs. 16-20 weeks for the standard regimen (see Tables 1 and 2, and Figure 2).[11-13] This is substantially shorter than time to relapse-free cure in murine studies supporting the successful S31 trial, and the ongoing A5362 trial, in which CFZ and rifapentine achieved cure at 10 to 12 weeks.[14-16] The following measures will minimize risk to participants: individual participants will be closely monitored clinically and bacteriologically, and a Data and Safety Monitoring Board will review trial progress regularly. In addition, participants will be followed closely for relapse after discontinuing experimental therapy. Sputum will be collected for TB culture at every study visit, including up to 74 weeks after completion of experimental therapy, when most relapses are expected to occur. Participants in the experimental arm with evidence of poor clinical response will be retreated with standard TB therapy.

The experimental regimen could have greater toxicity than the standard regimen. This is unlikely given that all drugs in the *PRESCIENT* experimental regimen are widely used in DR-TB treatment with excellent tolerability and infrequent serious adverse drug reactions. The conduct and safety of the study will be monitored via regular summaries of accrual rates, deaths, SAEs, AEs, and study discontinuation, as described in the Study Progress, Data, and Safety Monitoring Plan. Moreover, the Data and Safety Monitoring Board will review safety data regularly. Confidentiality risks will be minimized through the procedures described in Section 9.5.

1.4.2 Safety of Experimental Group Medications

1.4.2.1 *Bedaquiline*: The rate of treatment-related adverse events, including transaminase elevations, was similar between BDQ and placebo groups in registrational Phase IIb trials, including overall adverse events and treatment-related Grade 3 or 4 adverse events.[59,60] In the Phase IIb NC-005 trial there were no excess AEs, including Grade 3 events, SAEs, and liver-related events, among DS-TB participants randomized to BDQ-containing regimens (n = 121) for 56 days.[53] The same BDQ dosing regimen as *PRESCIENT*, 200 mg daily, was used in one of the NC-005 arms and in the successful SimpliciTB trial. BDQ is associated with QTc prolongation. In Phase II clinical trials of BDQ, mean maximum increase in Fridericia-corrected QT interval (ΔQTcF) at 24 weeks ranged from 12 - 16ms,[59-61] with very few Grade 4 QT events and no clinically significant

dysrhythmias reported. Using rigorous ECG monitoring, severe QT-prolongation (QTcF ≥500ms) was uncommon (4/183 patients) with the combined use of BDQ and CFZ for DR-TB in a programmatic setting, and did not lead to permanent discontinuation of either drug; in that study, mean QTcF after 2 months of combination therapy was 421ms (SD 25.6), well below the cutoff for a Grade 3 or higher event.[37]

1.4.2.2 *Clofazimine*: The most common toxicity related to CFZ is non-melanotic hyperpigmentation (due to partitioning of the circulating, free base form of the drug into subcutaneous fat), phototoxicity, and ichthyosis; this is related to treatment duration and is reversible after stopping treatment, although detailed time course data are sparse.[62] Incidence of skin discoloration varies widely in clinical studies.[23,63-67] Intensity of skin and organ discoloration seems to correlate with treatment dose and duration in animal studies, but this has not been quantified or related to drug exposure.[68] One retrospective review of CFZ toxicity among DR-TB patients in South Africa did not find a significant difference in occurrence of skin discoloration between different dose-weight categories.[66] In a leprosy trial (n = 2,912) CFZ-related skin pigmentation during 6 months of treatment was usually short-lived and acceptable to patients.[69] A meta-analysis of cohort studies including 602 MDR-TB cases treated with CFZ reported a pooled proportion of adverse drug reactions requiring discontinuation of CFZ in 0.1%, comparable to that of first-line TB treatment.[70] Abdominal and epigastric pain, diarrhea, nausea, vomiting and gastrointestinal intolerance are also commonly reported. CFZ may also prolong the QTc interval, with mean QTcF prolongation of about 13ms at 14 days.[21]

1.4.2.3 *Pyrazinamide*: The most frequent adverse event of PZA is hepatotoxicity. Transient increases in serum aminotransaminase concentrations are frequent but usually self-limited and require no specific treatment.[71] Rarely, severe hepatitis and death have occurred.[72] Hepatotoxicity appears to be dose-related, and may occur at any time during therapy. PZA inhibits renal excretion of urates, frequently resulting in hyperuricemia. This effect is usually asymptomatic, but acute gout has occurred in some patients. These side effects are seldom dose-limiting. Minor arthralgias also may occur during PZA treatment.

1.4.2.4 *Delamanid*: DLM has moderate QT-prolonging potential, mean change in QTcF around 8 - 12ms at 8 weeks,[30,61] but serious QT prolongation is uncommon. In a Phase III trial, there was no difference in QTcF prolongation between participants receiving DLM and those receiving placebo, and QTcF >500 ms occurred in only 2.1% (7/341) in the DLM arm with no clinically significant arrhythmias reported.[73] Hepatitis has been infrequently reported with DLM. In the Phase III trial for DR-TB

therapy, the rate of transaminase elevations was similar in the DLM and placebo groups.

1.4.2.5 *Combination Therapy*: All drugs in the experimental regimen are widely used in DR-TB treatment, often in combination. Potential adverse events of concern relating to combination therapy are hepatoxicity (all drugs) and QT prolongation (BDQ, CFZ, DLM).

Hepatotoxicity: Hepatotoxicity has been infrequently reported with BDQ and DLM in clinical trials and programmatic settings.[73,74] The multi-country endTB observational study, involving over 2,300 patients with DR-TB in programmatic settings, where BDQ, DLM, and CFZ were provided to 70%, 40%, and 70%, respectively, Grade 3 or higher hepatotoxicity was reported in only 5.5%, occurring at a median of 3.1 months.[75]

QTc Interval Prolongation: CFZ, BDQ, and DLM each prolong the QT interval, but these drugs are frequently used in combination in the current treatment of DR-TB without major safety signals. The A5343 trial provided reassurance for the safety of co-administration of DLM with BDQ, showing clinically modest increases in QTcF and no reported Grade 3 or 4 QT prolongation events.[76] QT events were also infrequent in the endTB observational study (n = 2296) where 96% of participants received BDQ or DLM plus at least one other QT-prolonging drug (CFZ in 70%): only 2.7% experienced any QTcF ≥500 ms or ΔQTcF >60 ms with serious arrythmia, with events occurring at a median time of 2.5 months (1.8 events/1000 person-months (95% CI: 1.4-2.3).[75] Taken together, these data suggest a low risk of serious QT events with the experimental regimen, especially given the short duration of therapy. We shall, however, implement systems for robust ECG monitoring and reporting, including after treatment discontinuation to account for long half-life drugs.

1.4.3 Safety of Standard Group Medications

1.4.3.1 *Rifampin:* Rifampin is well tolerated at standard doses. It often causes harmless but disconcerting red-orange discoloration of tears, sweat, saliva, feces, and urine. Less than 4% of TB patients experience significant adverse reactions to rifampin. Gastrointestinal side effects are the most common, and they include epigastric distress, anorexia, nausea, vomiting, cramps, and diarrhea. Hepatitis rarely occurs in persons who have normal baseline hepatic function. The incidence of hepatitis may be increased for older persons and those who have chronic liver disease or alcoholism, but remains lower than that for pyrazinamide or isoniazid.[71,72] Rifampin can cause a flu-like syndrome of fever, chills, and myalgia, although this is uncommon using standard doses given daily. In a very small proportion of

patients, the flu-like syndrome is associated with interstitial nephritis, acute tubular necrosis, thrombocytopenia, hemolytic anemia, and shock.

1.4.3.2 *Isoniazid*: The total incidence of all adverse effects from isoniazid is approximately 5%, most of which do not require discontinuation of the drug. Peripheral neurotoxicity is dose dependent but is uncommon (<0.2%) at conventional doses. The risk of peripheral neuritis increases for persons who are malnourished or predisposed to neuritis by other illnesses. Other nervous system reactions are rare at normal doses, and they include convulsions, encephalopathy, optic neuritis, memory impairment, and psychosis. Gastrointestinal adverse effects include nausea, vomiting, and epigastric distress. Asymptomatic elevation of aminotransferases is common and occurs in 10-20% of persons receiving isoniazid.[71] Idiosyncratic severe hepatic reactions are uncommon but are more likely in older persons (persons more than 50 years of age).[72]

1.4.3.3 *Pyrazinamide*: The most frequent adverse event of PZA is hepatotoxicity. Transient increases in serum aminotransaminase concentrations are frequent, and usually self-limited and require no specific treatment.[71] Rarely, severe hepatitis and death have occurred.[72] Hepatotoxicity appears to be dose-related, and may occur at any time during therapy. PZA inhibits renal excretion of urates, frequently resulting in hyperuricemia. This effect is usually asymptomatic, but acute gout has occurred in some patients. These side effects are seldom dose-limiting. Minor arthralgias also may occur during pyrazinamide treatment.

1.4.3.4 *Ethambutol*: Ethambutol is usually well-tolerated with low rates of skin rash, nausea, vomiting, or diarrhea. Fever, allergic reactions, abdominal pain, mental status changes, peripheral neuropathy, and increased liver function tests have rarely been associated with ethambutol.[71] Adverse events occur in less than 2% of patients receiving ethambutol and include decreased visual acuity (0.8%), rash (0.5%) and asymptomatic hyperuricemia. The most common serious side effect of ethambutol is retinal toxicity, often first perceived as a decrease in color perception. Rates of retinal toxicity are extremely low when the drug is given for relatively short periods at standard doses.

1.4.4 Potential Benefits

Participants may not derive direct benefit from the trial. However, for individuals in the experimental arm, there is the possibility of a shortened treatment regimen. Additionally, all participants may benefit from more regular monitoring during TB treatment, including monitoring the effects of standard TB treatment and the disease itself. Adherence support will be provided to all individuals in the trial. More broadly, participants will be adding to generalized knowledge about the treatment of drug-susceptible pulmonary TB, which could benefit the study population.

2 STUDY DESIGN, OBJECTIVES, OUTCOME MEASURES

2.1 Study Design Description

This is a Phase IIc, open-label, multi-center, randomized controlled trial to evaluate the microbiological efficacy of a rifamycin-free ultra-short regimen for DS-TB. The study population includes 156 adults (≥18 years) with confirmed smear-positive drug-susceptible pulmonary TB, with or without HIV. Patients with HIV are eligible if they have CD4 counts ≥200 cells/mm^3, if they are receiving ART or plan to initiate ART within 8 weeks after enrollment. Enrollment of patients with HIV will be limited to 20% (n = 32) of the total study population. The initial 25% of enrollment will be restricted to participants (n = 39) with mild or moderate disease, defined as having sputum with higher Xpert MTB/RIF cycle threshold (Ct) values (> 17 cycles) and the absence of extensive lung disease on chest X-ray (involvement of at least half of the area of the entire thoracic cavity). Thereafter, all eligible patients will be offered participation without a pause in enrollment.

Eligible participants will be randomized in a 1:1 ratio to BCZD or standard anti-TB therapy. Randomization will be stratified by presence of lung cavitation and HIV status. Treatment in the standard arm will be provided for 26 weeks (8 weeks of RHZE followed by 18 weeks of RH). Treatment in the experimental arm will be provided for 12 weeks. See Table 4 for dosing in the BCZD and standard groups, and Figure 1 for the study schema.

Patients with evidence of poor clinical response (see Section 6.4) will be transitioned to standard TB therapy. Adherence will be monitored using electronic adherence monitoring devices or directly observed therapy.

The primary analysis will be a superiority efficacy comparison of time to liquid culture conversion through 8 weeks in each experimental arm compared with the standard therapy arm. Participants will have extended post-treatment follow up to evaluate definitive clinical endpoints of treatment failure, relapse, and death as a secondary composite outcome measure at 60 weeks after randomization, (48 weeks after completion of experimental therapy), when most relapses are expected to occur.[77]

2.2 Study Objectives

2.2.1 Primary Objective

2.2.1.1 To compare time to liquid culture conversion through 8 weeks for BCZD vs. standard treatment in HIV-positive and -negative adults with DS-TB.

2.2.2 Secondary Objectives

2.2.2.1 To compare safety (adverse events) and tolerability over 60 weeks.

2.2.2.2 To compare cumulative probability of experiencing favorable composite outcome (defined in section 9.2) at 60 weeks between participants treated with BCZD vs. with standard treatment.

2.2.2.3 To detect treatment-emergent resistance with BCZD

2.2.2.4 To compare time to liquid culture conversion through 12 weeks for BCZD vs. standard treatment.

2.2.2.5 To compare time (days) to positivity in liquid culture over 8 weeks.

2.2.3 Exploratory Objectives

2.2.3.1 To compare cumulative probability of experiencing favorable composite outcome (defined in section 9.2) at 86 weeks between participants treated with BCZD vs. with standard treatment.

2.2.3.2 To explore the effect of drug exposure, derived from population PK models based on observed concentrations, on time to culture positivity as a pharmacodynamic measure of mycobacterial burden and treatment response, and on QTcF prolongation.

2.2.3.3 To compare post-tuberculosis pulmonary sequelae between BCZD vs. standard group participants with the use of spirometry, chest radiographs, respiratory and quality of life questionnaires, and biomarkers.

2.2.3.4 To assess the association between food insecurity and time to culture conversion and probability of experiencing a favorable composite outcome (defined in section 9.2) at 86 weeks in both groups.

2.2.3.5 To collect blood (and its derivatives), sputum and oral swabs for potential future use in diagnostic, biomarker, or PK analyses.

2.3 Outcome Measures

2.3.1 Primary Outcome Measure

2.3.1.1 Time to stable liquid culture conversion [Time Frame: Measured through Week 8]
Defined as the first of two negative sputum cultures, consecutive or not, without an intervening positive culture, and/or visits wherein the participant is unable to produce sputum and has no signs or symptoms of active TB.

2.3.2 Secondary Outcome Measures

2.3.2.1 Proportion experiencing any Grade 3 or higher AE including any occurrence that is new in onset or aggravated at least one-grade from baseline [Time Frame: Measured at Week 60]
Graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, July 2017.

2.3.2.2 Proportion with favorable composite outcome [Time Frame: Measured at Week 60]
Additional details in section 9.2.

2.3.2.3 Proportion who prematurely discontinue treatment [Time Frame: Measured at Week 12 in Arm 1 and Week 26 in Arm 2]

2.3.2.4 Time to stable liquid culture conversion [Time Frame: Measured through Week 12]
Defined as the first of two negative sputum cultures, consecutive or not, without an intervening positive culture, and/or visits wherein the participant is unable to produce sputum and has no signs or symptoms of active TB.

2.3.2.5 Mean subjective 'change in coloration' score at weeks 8, 12, 16, 26, 60 and 86 in Arm 1 vs. Arm 2 (10-point numeric rating scale) [Time Frame: Measured at Weeks 8, 12, 16, 26, 60, and 86]
10-point numeric rating scale where 0=none, 10=worst possible change in coloration.

2.3.2.6 Mean subjective 'distress related to skin coloration' score at weeks 8, 12, 16, 26, 60, and 86 in Arm 1 vs. Arm 2 (10-point numeric rating scale) [Time Frame: Measured at Weeks 8, 12, 16, 26, 60, and 86]
10-point numeric rating scale where 0=none, 10=worst possible distress due to coloration.

2.3.2.7 Mean change in QTcF from baseline to week 1, 2, 4, 8, 12, and 16 [Time Frame: Measured at Week 1, Week 2, Week 4, Week 8, Week 12, and Week 16]
The QTcF is derived from ECG readings, which the sites conduct in triplicate (three ECGs 5-10 minutes apart). The mean of all measurements (up to 3) that are readable and available will be used at each of baseline (screening visit), week 1, week 2, week 4, week 8, week 12 and week 16.

2.3.2.8 Mean change in QTcF from baseline to end of treatment [Time Frame: Measured at week 12 in Arm 1]
The QTcF is derived from ECG readings, which the sites conduct in triplicate (three ECGs 5-10 minutes apart). The mean of all measurements (up to 3) that are readable and available will be used at baseline (screening visit), week 12 (Arm 1).

2.3.2.9 Occurrence of absolute QTcF >480 ms and ≤500 ms, and >500 ms [Time Frame: Measured through Week 16 in Arm 1 and Arm 2]
The QTcF is derived from ECG readings, which the sites conduct in triplicate (three ECGs 5-10 minutes apart). The mean of all measurements (up to 3) that are readable and available will be used through week 16 (Arms 1 and 2).

2.3.2.10 Occurrence of QTcF change from baseline of >30 ms and ≤60 ms, and >60 ms [Time Frame: Measured through Week 16 in Arm 1 and Arm 2]
The QTcF is derived from ECG readings, which the sites conduct in triplicate (three ECGs 5-10 minutes apart). The mean of all measurements (up to 3) that are readable and available will be used through week 16 (Arm 1 and 2)).

2.3.2.11 Proportion of participants with one or more serious adverse events (SAEs) [Time Frame: Week 86]
Serious adverse events reported at any time during participation in the trial.

2.3.2.12 Proportion with culture conversion in liquid and solid media (separately) at weeks 4, 8 and 12 after randomization [Time Frame: Measured at Weeks 4, 8, and 12].
Proportion of participants who have achieved stable culture conversion, defined as two negative sputum cultures, consecutive or not, without an intervening positive culture and/or visits wherein the participant is unable to produce sputum and has no signs or symptoms of active TB; occurring before or at the week 4, 8, or 12 visit, respectively.

2.3.2.13 Proportion with TB relapse (by *M. tuberculosis* genotyping) from initiation of treatment to 86 weeks. [Time Frame: Measured at Week 86]
For participants who had successful culture conversion through the end of study treatment, TB relapse is defined as a recurrence of TB emanating from the same strain as the participant's originally diagnosed TB, which will be determined through whole genome sequencing.

2.3.2.14 Proportion of treatment-emergent genotypic and phenotypic resistance to BCZD. [Time Frame: Measured through Week 86]
For participants in Arm 1 only. MIC values will be evaluated against resistance-associated variants for paired baseline and failure isolates. Frequencies and proportions with phenotypic and/or genotypic resistance to any drug will be reported.

2.3.2.15 Time (days) to positivity in liquid culture (MGIT) after start of treatment across study arms [Time Frame: Measured through Week 8]
Median (Q1, Q3) times to positivity in liquid culture at each time point (weeks 1, 2, 3, 4, 6, and 8) in Arm 1 and Arm 2.

3 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

3.1 Study Product Description

Participants enrolled to the study will be randomized to receive one of the following drug regimens:

1. Experimental arm (Arm 1): BCZD for 12 weeks
2. Control arm (Arm 2): RHZE for 8 weeks, followed by RH for 18 weeks

The dosages are listed below in Table 4.

3.2 Formulation, Packaging, and Labeling

3.2.1 Experimental Group Medications

3.2.1.1 Bedaquiline:
Mechanism of action: BDQ is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP synthase, an enzyme that is essential for the generation of energy in *Mtb.*
Formulation: Each tablet contains 100mg of BDQ
Appearance: Uncoated white to almost white round biconvex tablets with debossing of "t" over "207" on one side and "100" on the other side.

3.2.1.2 Clofazimine:
Mechanism of action: The proposed mechanism of action of CFZ is redox cycling and toxic production of reactive oxygen species superoxide and H_2O_2, as well as increased lysophospholipid production resulting in inhibition of cellular uptake of K^+. These mechanisms interfere with ATP production resulting in bacterial cell wall dysfunction and death. CFZ also has anti-inflammatory effects thought to be due to decreased activation and proliferation of T-lymphocytes.[78,79]
Formulation: Each capsule contains 100mg of micronized clofazimine suspended in an oil-wax base.
Appearance: Soft gelatin capsule, which is brown and spherical

3.2.1.3 Pyrazinamide
Mechanism of action: The exact mechanism of action of PZA has not been fully elucidated. The antimycobacterial activity appears to partly depend on conversion of the drug to pyrazinoic acid (POA).
Formulation: Each tablet contains 500mg pyrazinamide.
Appearance: The appearance of PZA varies based on manufacturer.

3.2.1.4 Delamanid
Mechanism of action: The pharmacological mode of action of DLM involves inhibition of the synthesis of the mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid.

Formulation: Each film-coated tablet contains 50mg of DLM
Appearance: Round, yellow, film-coated tablet, 11.7mm diameter

3.2.2 Standard Medications

3.2.2.1 RHZE (Rifafour) and RH (Rifinah)
Mechanism of action: Combination therapy for the treatment of TB.
Formulation: RHZE: Each tablet contains rifampin 150mg, isoniazid 75mg, pyrazinamide 400mg, and ethambutol 275mg. RH: Each tablet contains rifampin 150mg and isoniazid 75mg
Appearance: The appearance varies based on manufacturer.

All study drugs will be packaged and labelled by trial pharmacists prior to dispensing. Packaging will be in the form of blister packs or packets. Depending on adherence monitoring plans for the site, packaged study drug may be inserted into Wisepill (or similar) devices at the time of dispensing.

3.3 Product Storage and Stability

Study drug will be stored according to manufacturer instructions. All storage rooms in the Research Pharmacies at the study sites are temperature regulated with air conditioners. An alarm is activated if a temperature out of range occurs.

3.4 Acquisition/Distribution

All study medications except for DLM will be purchased through the Global Drug Facility (GDF), except that BDQ will be purchased directly from Janssen Therapeutics for use in South Africa. DLM will be donated by Otsuka Pharmaceutical Co, Ltd.

3.5 Protocol-Specified Medications other than Study Products

3.5.1 Antiretroviral Therapy

Participants with HIV who are not already taking ART at enrollment will be initiated on ART in routine care according to WHO and local treatment guidelines. Antiretroviral medications are NOT provided through the study and must be obtained locally by the site. Selection and dosing of ART in combination with rifampicin should adhere to local guidelines at each site. Non-nucleoside reverse transcriptase inhibitors and protease inhibitors are disallowed.

3.5.2 Pyridoxine

As per local guidelines, participants in the standard group (Arm 2) will receive pyridoxine at a dose of 25mg oral daily to prevent peripheral neuropathy secondary to INH use. This may be increased to 100mg oral daily if indicated, according to WHO and local guidelines.

Pyridoxine (vitamin B6) will NOT be provided through the study and must be obtained locally by the site.

3.5.3 Prohibited Medications

A list of prohibited medications is provided in Appendix A. The list of QT-prolonging drugs can be found by consulting CredibleMeds (https://www.crediblemeds.org).

The following medications are disallowed, for each specific anti-tuberculosis drug, during treatment and up to 1 month after the end of treatment:

Bedaquiline
- Moderate and strong CYP3A4 inhibitors (e.g., ritonavir-boosted protease inhibitors; azole antifungals including ketoconazole, voriconazole, itraconazole; ketolides such as telithromycin; and macrolide antibiotics other than azithromycin);
- Moderate and strong CYP3A4 inducers (e.g., efavirenz, phenytoin, carbamazepine, phenobarbital, St. John's wort, rifampin and rifapentine).

Delamanid
- Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, St. John's wort, rifampin and rifapentine).

There are no additional absolute contraindications on medications delivered concomitantly with clofazimine or pyrazinamide.

3.6 Dosage and Administration of Study Investigational Product

BDQ 200 mg: will be administered as two capsules orally once daily with food for 12 weeks.

CFZ 300 mg: will be administered as three 100 mg capsules orally once daily with food for 2 weeks.

CFZ 100 mg: will be administered as one capsule orally once daily with food for 10 weeks.

PZA: will be administered based on weight (Table 4) orally once daily with food for 12 weeks [1000mg to 2000mg oral daily for 12 weeks (30-37 kg: 1000mg; 38-70 kg: 1500mg; >70kg: 2000mg)].

DLM 200 mg: will be administered as four capsules orally once daily with food for 12 weeks.

RHZE: administered at the same time on an empty stomach, 1 hour before or 2 hours after eating, orally once daily for 8 weeks.

RH: administered at the same time on an empty stomach, 1 hour before or 2 hours after eating, orally once daily for 18 weeks.

Table 4. Dosing in the Experimental and Control Arms

WHO Weight Range Bands	30 – 37 kg	38 – 54 kg	55- 70 kg	> 70 kg
BCZD Group				
BDQ	200 mg daily			
CFZ	300 mg daily for 2 weeks, followed by 100 mg daily for 10 weeks			
PZA	1000 mg daily	1500 mg daily		2000 mg daily
DLM	200 mg daily			
Standard Group				
RIF	300 mg	450 mg	600 mg	750 mg
INH	150 mg	225 mg	300 mg	375 mg
PZA	800 mg	1200 mg	1600 mg	2000 mg
EMB	550 mg	825 mg	1100 mg	1375 mg

3.7 Accountability Procedures for the Study Investigational Products

Once received, the study medications will be stored in the research pharmacies, and dispensed by the research pharmacists. The pharmacist of record for the study at each site will ensure that the investigational products are appropriately managed, with SOPs to ensure ordering, receipt, storage, security, labeling, dispensing, reconciliation, disposition, and accountability of all study products. At study termination, all unused investigational product will be disposed in accordance with pharmacy SOPs following complete drug accountability and monitoring.

4 SELECTION OF PARTICIPANTS AND STUDY ENROLLMENT AND WITHDRAWAL

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

Individuals must meet all the inclusion criteria in order to be eligible to participate in the study.

4.1.1.1 Informed consent obtained and signed.

4.1.1.2 Male or female, aged ≥18 years.

4.1.1.3 Pulmonary TB diagnosed by Xpert MTB/RIF, Xpert MTB/RIF Ultra, Line Probe Assay (LPA), or mycobacterial culture.

4.1.1.4 Sputum positive for acid fast bacilli (at least 1+ grade on the WHO scale).

4.1.1.5 Pulmonary TB diagnosed without known INH resistance (by LPA or Xpert MTB/XDR) and without known RIF resistance (by either LPA or Xpert). Note that phenotypic DST for INH resistance will be done on screening cultures (using MGIT). If baseline molecular or phenotypic test results that become available after enrollment detect resistance to INH or RIF, the participant will be a late exclusion from the study.

4.1.1.6 Newly diagnosed with TB and have a history of being untreated for at least 6 months after cure from a previous episode of TB.

4.1.1.7 For participants living with HIV, CD4+ cell count ≥200 cells/mm^3, obtained within 30 days prior to study entry.

4.1.1.8 For participants living with HIV, must be currently receiving or planning to initiate ART at or before study week 8.

4.1.1.9 Laboratory values at study screening:

- Alanine aminotransferase (ALT)[1] ≤3x the upper limit of normal (ULN)
- Total bilirubin ≤2.5 x ULN
- Creatinine ≤2 x ULN
- Potassium ≥3.5 mEq/L, ≤5.5 mEq/L
- Absolute neutrophil count (ANC) ≥650/mm^3
- Hemoglobin ≥7.0g/dL
- Platelet count ≥50,000/mm^3

[1] Serum or plasma

4.1.1.10 For females of reproductive potential, negative serum or urine pregnancy test within 5 days prior to entry and willingness to use effective contraception for the first 60 weeks of the study, as well as during re-treatment (if re-treatment indicated). Female participants who are not of reproductive potential must have documentation of menopause, hysterectomy, or bilateral oophorectomy or bilateral tubal ligation. Acceptable forms of contraception include: condoms, intrauterine device or intrauterine system, cervical cap with spermicide, diaphragm with spermicide.

4.1.2 Exclusion Criteria

Patients meeting any of the exclusion criteria at baseline will be excluded from study participation.

4.1.2.1 More than 5 days of treatment directed against active TB for the current TB episode preceding study entry.

4.1.2.2 Current extrapulmonary TB (e.g. neurological, skeletal, abdominal), not including pleural TB, in the opinion of the site investigator.

4.1.2.3 Pregnant or breastfeeding.

4.1.2.4 Weight <30kg.

4.1.2.5 Inability to take oral medications.

4.1.2.6 Current or planned use of any drug known to severely prolong the QTc interval, including, but not limited to: amiodarone, amitriptyline, chloroquine, chlorpromazine, cisapride, disopyramide, erthyromycin, moxifloxacin, procainamide, quinidine, or sotalol.

4.1.2.7 Current or planned use of one or more of the following HIV medications: HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, elvitegravir/cobicistat, or bictegravir.

4.1.2.8 Current or past use of clofazimine, bedaquiline or delamanid.

4.1.2.9 QTcF >450ms for men or >470 ms for women.

4.1.2.10 Current or history of known personal or family long QT syndrome.

4.1.2.11 Known allergy/sensitivity to components of study TB drugs or their formulation.

4.1.3 Late Exclusion

Microbiologic confirmation of drug-susceptible TB is not always available at the time of enrollment. Enrolled individuals who are subsequently determined to meet either of the following criteria will be classified as late exclusions and study treatment will be discontinued. These participants will be transitioned to routine care but requested to remain in study follow up for safety evaluations.

A. Screening, baseline study, and Week 1 visit sputum cultures fail to grow *M. tuberculosis*.
B. Resistance to RIF or INH is detected from baseline molecular or phenotypic testing results that become available after enrollment.

4.2 Withdrawal, Discontinuation of Study Product, or Study Termination

4.2.1 Withdrawal from the Study or Discontinuation of the Study Product

Participants may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled. An investigator may also withdraw a participant from receiving the study product, after discussions with the Clinical Management Committee (CMC). Follow-up safety evaluations will be conducted, if the participant agrees. If a participant withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms (CRFs).

Reasons for treatment discontinuation might include, but are not limited, to the following:

- Serious drug-related toxicity (see section 7.1).
- Requirement for prohibited concomitant medications (see section 3.5).
- Completion of treatment as defined in the protocol.
- Request by participant to terminate treatment.
- Determined by a physician's discretion to require additional therapy not indicated in the protocol to ensure participant's health and well-being (or treatment failure, if applicable).
- Pregnancy or breastfeeding.

If a participant in the experimental group becomes pregnant, she will be discontinued from study medications and re-treated with standard medication for the treatment of TB and referred to a prenatal care program for management of her pregnancy according to local standards of care; women in the standard group who become pregnant will receive the same care as the experimental group, except they will continue standard TB medication. Women living with HIV will be referred to their local HIV clinic for appropriate care. Women will be followed through the end of the study period. At the end of the pregnancy, the outcome and AEs for the participant and the infant will be recorded on the outcome eCRFs. If a female participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on the eCRFs at the end of the pregnancy.

The investigator should be explicit regarding study follow-up (e.g. safety follow-up) that might be carried out despite the fact the participant will not receive further study product. If the participant consents, every attempt will be made to follow all AEs through resolution.

The investigator will inform the participant that already collected data will be retained and analyzed even if the participant withdraws from this study.

4.2.2 Participant Replacement

Participants who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the informed consent form and administration of the study product will not be replaced.

4.2.3 Study Termination

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study participants and assure appropriate therapy or follow-up for the participants, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB and regulatory authorities.

5 STUDY PROCEDURES

5.1 Screening

Potential participants will be identified at the time of TB diagnosis, based on a positive Xpert MTB/RIF Ultra or *Mtb* smear/culture performed as part of routine care. Interested individuals will be provided with study information, including the risks and potential benefits. If the potential participant understands the key information about the study, and is willing to participate, they will be asked to consent to participate in the study. Informed consent will be obtained prior to conducting any study-related activities. At screening, the following evaluations will take place:

5.1.1 Clinical Evaluation

- History: include current receipt of components of study TB drugs, ability to take oral medications, HIV status, symptoms of extrapulmonary TB
- Examination: weight, signs of extrapulmonary TB

5.1.2 Laboratory Investigations

- If HIV status is unknown: rapid HIV test x 1 plus HIV ELISA or a second rapid HIV test from a different manufacturer to confirm positive results
- If HIV-positive, CD4 count
- Pregnancy test (urine or serum) in women of childbearing potential
- Liver function tests (ALT, AST, alkaline phosphatase, bilirubin)
- Serum potassium
- Serum creatinine
- Complete blood count (CBC) and differential count
- Sputum AFB smear
- Sputum Xpert Mtb/Rif Ultra, if not done as part of routine care within 30 days prior to entry (or the routine care result is not available to the study).
- Liquid and solid TB culture on sputum
- Hain LPA MTBDR*plus* (or sputum Xpert MTB/XDR), if not done within 30 days prior to entry, and phenotypic DST for INH on appropriate specimens
- ECG (triplicate)
- Chest X-ray (CXR)

Screening tests must be performed within 30 days prior to enrollment, except for those screening tests which must be performed within 5 days prior to enrollment (see Table 5). Patients must have taken no more than 5 days of TB treatment prior to enrollment.

5.2 Entry

Informed consent must be obtained prior to study screening. The results from screening will be reviewed to confirm whether participants are eligible to take part in the trial. The results of the

pregnancy test and other lab investigations must be available prior to enrollment. At enrollment, the following evaluations will take place:

5.2.1 Clinical Evaluation

- History: focused medical history and medication review
- Examination: vital signs and complete clinical examination

5.2.2 Laboratory and Radiographic Investigations

- If HIV-positive, plasma HIV-1 RNA
- Hemoglobin A1c (HbA1c)
- C-reactive protein
- Oral swab, blood, sputum and urine storage
- Sputum collection for AFB smear, liquid and solid culture, MTB storage, MIC testing*, MTB DNA extraction*

*For Arm 1 participants only

Randomization will occur at the Entry visit after reviewing results from screening procedures and final eligibility confirmation by a study investigator (described in section 9.4.1).

5.3 Planned Study Visits

See Table 5 for a summary of the components of screening and follow-up visits. Study visits are anticipated to take approximately 2 hours of participant participation. The allowable window for study visits during the experimental treatment period is +/- 3 days, during the continuation phase of control treatment is +/- 5 days, and during the post-treatment follow-up period is +/- 7 days.

Table 5. Schedule of Events

Visit	Screening	Entry	Treatment weeks (window ± 3 days)								Treatment weeks (window ± 5 days)			Follow up (window ± 7 days)					Time of treatment failure/relapse/ recurrence[k]	Premature Treatment/ Study Discontinuation
	-30 to 0	0	1	2	3	4	6	8	10	12	16	20	26	36	48	60	72	86		
HIV status confirmation	X																			
Clinical evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X[a]		*If clinically indicated*																	
HbA1c		X																		
Liver function tests	X[a]			X		X	X	X	X	X	X		X							X
Chemistry (electrolytes)	X[a]			X		X		X		X	X		X							X
Hematology	X[a]			X		X		X		X			X							
C-reactive protein		X		X						X			X							
CD4+ count (if HIV-positive)	X																			
Plasma HIV-1 RNA (if HIV-positive)		X														X		X		
PK sampling (sparse)[b]				X				X		X	X									
PK sampling (intensive)[c]			X							X										
Blood stored for future testing		X	X	X		X		X		X			X						X	X
Urine stored for future testing		X		X				X		X			X						X	X
Sputum stored for future testing[d]		X	X	X		X		X		X			X						X	
Oral swab stored for future testing[e]		X	X	X		X		X		X			X			X		X	X	
Sputum AFB smear and culture[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Molecular assay to detect *Mtb* INH- and RIF-resistance[g]	X																			
Phenotypic DST for INH resistance	X																			
MIC testing[h]		X																	X	
Whole genome sequencing[i]		X																	X	
ECG (triplicate)	X		X	X		X		X		X	X									X
Subjective skin assessment								X		X	X		X			X		X		X
Adherence assessment			X	X	X	X	X	X	X	X	X	X	X							X
COPD Assessment Test			X							X			X			X		X		
Modified MRC Dyspnea Scale			X							X			X			X		X		

WHOQOL-BREF Questionnaire			X							X			X			X		X		
Food Insecurity Questionnaire			X							X			X			X		X		
Chest X-ray	X									X			X			X		X	X	
Spirometry[j]										X[i]			X			X		X		

a Must be done within 5 days prior to study entry
b Sparse PK timing to coincide with ECG recording around the time of expected maximal concentration (Cmax, 3 - 5 hours post-observed dose) - Arm 1 only
c Intensive PK sampling (paired venous blood and capillary finger prick) in 15 participants in Arm 1; pre-dose, and at 1, 2, 3, 4, 6, 8-10, and 24 hours after witnessed drug intake and an overnight fast. Ensure that participants are still on experimental therapy at the time of the PK visit. Only at the Cape Town site.
d Sputum collection for storage will be conducted if feasible, and after the collection of sputum for protocol-defined AFB and culture; Only the Cape Town site will collect sputum for storage at Week 26
e Oral swabs are an optional test; they will be conducted if logistically feasible; At weeks 1, 2, 4, 8, and at time of treatment failure/relapse/recurrence oral swabs will only be done at the Cape Town site.
f Two sputum samples for AFB smear microscopy and culture in liquid and solid media will be collected at each time point. Sputum specimens and culture isolates will be stored for further testing in the event of TB treatment failure or recurrence.
g Hain LPA MTBDR*plus* or Xpert MTB/XDR will be performed prior to or at screening for all participants; Xpert Mtb/Rif Ultra will be performed at screening if not already done as part of routine care.
h MIC testing will be done on all baseline isolates in Arm 1 as well as isolates reflecting treatment failure or relapse
i WGS will be done on isolates reflecting treatment failure or relapse and paired baseline isolates in Arm 1
j Spirometry will be conducted at these visits if it is logistically and clinically feasible; Only the Haiti site will conduct spirometry at Week 12
k Defined in section 6.4

5.3.1 Follow-up

5.3.1.1 Week 1

- Duration of visit: Approximately 1 hour
- Procedures:
    - Vital signs
    - Focused medical history and medication review
    - Focused clinical examination
    - Adherence assessment
    - COPD Assessment Test
    - mMRC Dyspnea Scale
    - WHOQOL-BREF Questionnaire
    - Food Insecurity Questionnaire
    - ECG (triplicate)
    - Intensive PK sampling for subgroup of 15 participants, described below
    - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage
    - Oral swabs (Cape Town site only), blood and sputum storage

5.3.1.2 Week 2

- Duration of visit: Approximately 3 - 5 hours
- Procedures:
    - Vital signs
    - Focused medical history and medication review
    - Focused clinical examination
    - Adherence assessment
    - Bloods: Creatinine, potassium, ALT, AST, bilirubin, CBC and differential count, and C-reactive protein
    - Sparse PK sampling (3 - 5 hours post-dose)
    - Oral swabs (Cape Town site only), blood, sputum, and urine storage
    - ECG (triplicate) at time of sparse PK sampling
    - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.1.3 Week 3

- Duration of visit: Approximately 1 hour
- Procedures:
    - Vital signs
    - Focused medical history and medication review
    - Focused clinical examination
    - Adherence assessment
    - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.1.4 Week 4

- Duration of visit: Approximately 1 hour
- Procedures:
    - Vital signs
    - Focused medical history and medication review
    - Focused clinical examination
    - Adherence assessment
    - Bloods: Creatinine, potassium, ALT, AST, bilirubin, CBC and differential count
    - ECG (triplicate)
    - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage
    - Oral swabs (Cape Town site only), blood and sputum storage

5.3.1.5 Week 6

- Duration of visit: Approximately 1 hour
- Procedures:
    - Vital signs
    - Focused medical history and medication review
    - Focused clinical examination
    - Adherence assessment
    - ALT, AST, bilirubin
    - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.1.6 Week 8

- Duration of visit: Approximately 3 - 5 hours
- Procedures:
    - Vital signs
    - Focused medical history and medication review
    - Focused clinical examination
    - Subjective skin assessment
    - Adherence assessment
    - Blood: Creatinine, potassium, ALT, AST, bilirubin, CBC and differential count
    - Sparse PK sampling (3 - 5 hours post-dose)
    - Oral swabs (Cape Town site only), blood, sputum, and urine storage
    - ECG (triplicate) at 3 - 5 hours post-dose
    - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.1.7 Week 10

- Duration of visit: Approximately 1 hour
- Procedures:
    - Vital signs
    - Focused medical history and medication review
    - Focused clinical examination
    - Adherence assessment
    - ALT, AST, bilirubin
    - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.1.8 Week 12

- Duration of visit: Approximately 3 - 5 hours
- Procedures:
    - Vital signs
    - Focused medical history and medication review
    - Focused clinical examination
    - Subjective skin assessment
    - Adherence assessment
    - COPD Assessment Test
    - mMRC Dyspnea Scale
    - WHOQOL-BREF Questionnaire
    - Food Insecurity Questionnaire
    - Blood: Creatinine, potassium, ALT, AST, bilirubin, CBC and differential count, and C-reactive protein
    - Sparse PK sampling (3 - 5 hours post-dose)
    - Intensive PK sampling for subgroup of 15 participants, described below
    - Oral swabs, blood, sputum, and urine storage
    - ECG (triplicate) at 3 - 5 hours post-dose
    - CXR
    - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage
    - Spirometry (Haiti only)

5.3.1.9 Week 16

- Duration of visit: Approximately 1 hour
- Procedures:
    - Vital signs
    - Focused medical history and medication review
    - Focused clinical examination
    - Subjective skin assessment
    - Adherence assessment

- Blood: Creatinine, potassium, ALT, AST, bilirubin
- Sparse PK sampling (random sample)
- ECG (triplicate)
- Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.1.10 Week 20

- Duration of visit: Approximately 1 hour
- Procedures:
  - Vital signs
  - Focused medical history and medication review
  - Focused clinical examination
  - Adherence assessment
  - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.1.11 Week 26

- Duration of visit: Approximately 1 hour
- Procedures:
  - Vital signs
  - Focused medical history and medication review
  - Focused clinical examination
  - Subjective skin assessment
  - Adherence assessment
  - COPD Assessment Test
  - mMRC Dyspnea Scale
  - WHOQOL-BREF Questionnaire
  - Food Insecurity Questionnaire
  - Blood: Creatinine, potassium, ALT, AST, bilirubin, CBC and differential count, and C-reactive protein
  - Oral swabs, blood, sputum (Cape Town site only), and urine storage
  - CXR
  - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage
  - Spirometry

5.3.1.12 Weeks 36, 48, and 72

- Duration of visit: Approximately 1 hour
- Procedures:
  - Vital signs
  - Focused medical history and medication review
  - Focused clinical examination

- Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.1.13 Weeks 60 and 86

- Duration of visit: Approximately 1 hour
- Procedures:
  - Vital signs
  - Focused medical history and medication review
  - Focused clinical examination
  - Subjective skin assessment
  - COPD Assessment Test
  - mMRC Dyspnea Scale
  - WHOQOL-BREF Questionnaire
  - Food Insecurity Questionnaire
  - Plasma HIV-1 RNA
  - Oral swab storage
  - CXR (unless performed within the previous 2 weeks)
  - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage
  - Spirometry

5.3.1.14 Premature Treatment/ Study Discontinuation

- Duration of visit: Approximately 1 hour
- Procedures:
  - Vital signs
  - Focused medical history and medication review
  - Focused clinical examination
  - Subjective skin assessment
  - Adherence assessment
  - Blood: Creatinine, potassium, bilirubin, ALT, AST
  - Blood and urine storage
  - ECG (triplicate)
  - Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.1.15 Treatment Failure/Relapse/Recurrence

- Procedures:
  - Vital signs
  - Focused medical history and medication review
  - Focused clinical examination
  - Oral swabs (Cape Town site only), blood, sputum, and urine storage
  - MIC testing
  - Whole genome sequencing

- CXR
- Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage

5.3.2 Final Study Visit

The final visit should occur 86 weeks after the participant's enrollment.

5.4 Unscheduled Study Visits

Unscheduled study visits will be documented on follow-up visit CRFs. The following may occur at unscheduled study visits:

- Vital signs
- Focused medical history and medication review
- Focused clinical examination
- Adherence assessment
- Assessment for SAE/AE – if suspected, refer for relevant investigations or consultations.
- Bloods: at clinician's discretion
- Sputum collection for AFB smear and liquid and solid culture, *Mtb* storage (at clinician's discretion)
- Investigations required for PPTR assessment (including CXR), at clinician's discretion, if applicable.

5.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions should be developed by the site and implemented promptly. It is the responsibility of the site Principal Investigator and other study personnel to use continuous vigilance to identify and report protocol deviations. All individual protocol deviations will be addressed in participant study records. Protocol deviations must be sent to the local IRB/IEC per its guidelines.

6 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

6.1 Clinical Evaluations

Clinical evaluations will be performed in accordance with the detailed Manual of Procedures.

6.1.1 Research Procedures

6.1.1.1 Medical history

a) Complete medical history
To be obtained at the Entry visit from the participant interview. It will cover current symptoms, including tuberculosis signs and symptoms, past medical history including prior tuberculosis history other health conditions and treatments (including HIV infection), medications (past and current) and allergies, social and occupational history, family history, habits and a systemic review.

b) Focused medical history
To be obtained at each follow-up visit. It will include new symptoms, medication adherence, new medications and a systemic review.

6.1.1.2 Subjective Skin Assessment

Participant-reported changes in skin pigment and distress specifically related to these changes will be assessed by verbal response to a 10-point numeric rating scale (NRS):

- Skin pigment change: 0 (none) to 10 (most significant possible)
- Distress related to skin pigment changes: 0 (none) to 10 (worst possible)

6.1.1.3 Questionnaires regarding respiratory status, quality of life, and food insecurity

a) COPD Assessment Test – 8-item questionnaire to measure the health status of patients with chronic obstructive pulmonary disease
b) Modified Medical Research Council Dyspnea Scale is a five-point scale used to assess the degree of functional disability due to dyspnea (Grade 0: I only get breathless with strenuous exercise; Grade 4: I am too breathless to leave the house or I am breathless when dressing/undressing)
c) World Health Organization, Quality of Life Questionnaire (WHOQOL-BREF): 26 items which address four domains: physical health, psychological health, social relationships, and environment, with two items measuring overall health and quality of life.
d) Food Insecurity Questionnaire: 8-item questionnaire to measure household or individual food security.

6.1.1.4 Clinical examination

a) Complete clinical examination
To be completed at the enrollment visit. It will include vital signs (temperature, blood pressure, pulse rate, respiratory rate), weight and height, plus general and systemic examination.

b) Focused clinical examination
To be completed at each follow-up visit. These examinations will be focused on new symptoms experienced by the participant. It will always include vital signs and may include other systems.

6.1.1.5 Electrocardiogram (ECG)

At all relevant visits, ECGs will be performed in triplicate (collection of three ECGs 5-10 minutes apart). After entry, the ECG should be performed 3-5 hours after dosing in Arm 1 during PK sampling at weeks 2, 8, and 12, and at any time at other visits and for Arm 2.

6.1.1.6 Chest X-ray (CXR)

Will take place at enrollment, follow-up visits, and time of treatment failure/relapse/recurrence (Table 5), according to site-level SOPs. Extent of disease (limited to one lobe or region, unilateral, bilateral, or diffuse) and cavitation status (cavities present [location] or absent) will be documented. For purposes of randomization stratification, the screening chest X-ray will be read, interpreted, and recorded at each site as cavitatory or non-cavitatory disease. Cavitation is defined as a gas-containing lucent space of at least 1cm in diameter within the lung parenchyma surrounded by an infiltrate or fibrotic wall greater than 1mm thick seen on CXR.

6.1.1.7 Spirometry

Spirometry will be conducted at Weeks 12 (Haiti only), 26, 60, and 86, according to the spirometry SOP if logistically and clinically feasible. Following a minimum of two acceptable spirometric maneuvers (ATS/ERS quality score A-C), the participant will receive 4 inhalations of albuterol 100mcg which will be administered via MDI and spacer. Post-bronchodilator spirometry will be conducted 15 minutes after albuterol administration.

6.1.2 Assessment of Concomitant Medications other than Study Product

The use of all non-study drugs (including over-the-counter medications) from 14 days before starting study drugs through the end of the study will be monitored and recorded. Particular attention will be paid to ensuring that participants are not prescribed any additional drugs with the potential to prolong the QT interval, and not prescribed medicinal products that are strong inducers of CYP3A4 (see Appendix A).

For HIV-positive patients not on treatment at enrollment, ART must be started within 8 weeks (ART is provided by routine care). ART must not include a protease inhibitor or a nucleoside reverse transcriptase inhibitor.

While on INH, participants must receive pyridoxine (vitamin B6) with each dose of INH based on current local, national or international dosing guidelines.

6.1.3 Assessment of Participant Compliance with Study Investigational Product

Treatment adherence will be monitored by either directly observed therapy or an electronic adherence-monitoring advice with real-time monitoring capability and alerts for missed doses using text messages and alarm reminders. Study staff will contact participants if no opening signal is recorded on a given day to ensure that treatment is taken 7 days a week.

6.1.4 Non-Research Standard of Care

Irrespective of the participant's participation in the research study, antituberculosis treatment is indicated. This includes RHZE for 2 months followed by RH for 4 months. Pyridoxine will be administered for the full 6 months. For HIV-positive participants, ART (and associated HIV care) will be provided and managed by routine care as per local guidelines.

6.2 Laboratory Evaluations

6.2.1 Clinical Laboratory Evaluations

6.2.1.1 Hematology

Blood will be drawn for a CBC with differential count, platelet count. This will require approximately 5mL of EDTA anticoagulated blood. Performed in real time at local laboratory.

6.2.1.2 Biochemistry

Blood will be drawn for measurement of creatinine, potassium, ALT, AST, and bilirubin. This will require approximately 5mL of blood. Performed in real time at local laboratory.

6.2.1.3 HIV Testing

Counseling prior to and following HIV testing and reporting of HIV testing results will follow local guidelines and regulations at each site. For study purposes, HIV-1 infection is defined as a positive result using any licensed rapid HIV test or any licensed HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit. Confirmation of the initial study test result is required and must utilize a different

method than the one used for the initial study assessment. The confirmatory study test must also be licensed and may include western blot, a second antibody test by a method other than the initial rapid HIV and/or E/CIA, HIV-antigen, or plasma HIV RNA viral load. Negative study HIV testing does not require confirmatory testing.

6.2.1.4 CD4 Count Testing

Individuals identified as being HIV-positive will have CD4 T cell count testing performed at the local laboratory unless the results are available for a test performed at or within 30 days prior to screening. This will require up to approximately 5 mL of blood .

6.2.1.5 HIV Viral Load Testing

Individuals identified as being HIV-positive will have HIV viral load measured unless the results are available for a test at or within 30 days prior to screening. This will require approximately 5 ml of blood. Testing can be by any method used routinely at the study site as a standard of care test.

6.2.1.6 Pregnancy Test

Serum or urine testing are acceptable. To be done within 72 hours of study entry and results must be available prior to administration of study product.

6.2.1.7 Obtaining Sputum Samples

Sputum may be spontaneously expectorated or induced by aerosol inhalation of sterile nebulized saline. Study sites will use their local procedure for sputum induction. Saliva should not be collected in place of a sputum specimen.

6.2.1.8 Sputum AFB Smear and Mycobacterial Culture in Liquid/Solid Media

Two sputum samples will be collected for smear and culture in liquid and solid medium at time points indicated in Table 5. Sputum AFB smear must be reported per WHO criteria (i.e., negative, scanty, +, ++, +++). Bacterial load will be determined and recorded for all specimens using the time to positivity output automatically provided by the mycobacteria growth indicator tube (MGIT) system. For all cultures demonstrating growth of AFB, species will be identified to at least the level of *Mtb* complex versus non-TB mycobacteria.

6.2.1.9 Molecular TB Diagnostic Assay (to detect *Mtb*)

Where available, WHO-endorsed molecular diagnostic TB assays (Xpert, Hain GenoType MTBDR*plus* v2.0 or greater (LPA), performed within 30 days prior to study entry for initial identification of *Mtb* will be documented.

6.2.1.10 Molecular and Phenotypic Assay to Detect *Mtb* INH- and RIF Resistance

Screening for resistance to RIF via Xpert MTB/RIF, Xpert MTB/RIF Ultra or Hain GenoType MTBDR*plus* is required to determine eligibility. Screening for INH

resistance through the Xpert MTB/XDR or Hain GenoType MTBDR*plus* is also required to determine eligibility. Phenotypic DST for INH resistance will be done on screening and/or entry cultures (using MGIT).

6.2.2 Research Assays

6.2.2.1 PK Sampling

Intensive PK sampling will be done for a subgroup of 15 consecutive participants randomized to Arm 1 at the Cape Town site. This will occur at Weeks 1 and 12 study visits where serial venous blood samples and paired capillary blood (finger prick) for volumetric absorptive micro-sampling (VAMS) will be collected pre-dose, and at 1, 2, 3, 4, 6, 8-10, and 24 hours after witnessed drug intake and an overnight fast. All participants randomized to the experimental group (Arm 1) across both sites (n = 78) will undergo sparse plasma PK sampling, coinciding with ECG recording around the time of expected maximal concentration (C_{max}, 3 - 5 hours post-observed dose) at study Weeks 2, 8, and 12, and a random sample at week 16 (volume 4 mL venous blood). Samples will be stored at -80˚C and shipped to the Division of Clinical Pharmacology at UCT to determine drug concentrations by LC-MS/MS assays.

6.2.2.2 Phenotypic Drug Susceptibility Testing and Whole Genome Sequencing

Mtb isolates from screening, enrollment, and all follow-up visits will be stored. Baseline isolates plus those recovered from Arm 1 participants with a positive culture at week 8 or later will undergo subculture and DNA extraction.

For Arm 1 participants experiencing treatment failure or relapse, MIC testing for all drugs (BCZD) and WGS will be performed on positive *Mtb* sputum cultures (1) at time points of treatment failure or relapse; and (2) on stored baseline (i.e., screening/entry) *Mtb* isolates. Variants will be annotated as resistance-associated if located at sites previously associated with resistance or in the presence of phenotypic resistance in this study.[80] Additional analyses will evaluate the similarity of infecting *Mtb* strains isolated from participants with treatment failure or relapse. Isolates with a SNP distance of <5 by WGS will be considered the same strain (rather than reinfection).

6.2.2.3 Samples for Future Analyses

Blood, sputum, oral swabs, and urine will be stored from all consenting participants for the purpose of future research to identify potential biomarkers, including human genetic analysis (South Africa only), of tuberculosis treatment response, and post-TB sequelae. Consenting patients will be asked to provide additional blood (approximately 10 ml blood per draw) at the entry visit and at week 1, week 2, week 4, week 8, week 12 and week 26 if logistically feasible. Samples should also be collected if a) failure or relapse is confirmed; and/or b) the participant voluntarily withdraws from the study. Consenting patients will be asked to provide urine at the

entry visit and at week 2, week 8, week 12 and week 26, if logistically feasible. Additionally, urine samples should also be collected if a) failure or relapse is confirmed; and/or b) the participant voluntarily withdraws from the study. Consenting participants will also be asked to provide sputum samples at the entry visit and at week 1, week 2, week 4, week 8, week 12, and week 26 (South Africa only) if logistically feasible. Additionally, sputum samples should also be collected if failure or relapse is confirmed. Consenting participants will also be asked to provide oral swabs at the entry visit, and at week 1 (South Africa only), week 2 (South Africa only), week 4 (South Africa only), week 8 (South Africa only), weeks 12, week 26, week 60, and week 86, if logistically possible. Additionally, oral swab samples should also be collected if failure or relapse is confirmed (South Africa only). Participant consent for stored specimens will be part of the study Informed Consent Form which will be administered during the Screening/Consenting visit, with one independent signature line for stored samples and one independent signature line for human genetic analysis (South Africa only).

6.2.2.4 Laboratory Specimen Preparation, Handling, and Storage

Specimen preparation and handling will be performed according to procedures set forth in the MOP.

6.2.2.5 Laboratory Specimen Shipping

Shipping will be performed by trained personnel according to the MOP and in accordance with local and international regulations and International Air Transport Association procedures. Specimens will be shipped to Stellenbosch University and University of Cape Town throughout the study.

6.3 Loss to Follow-Up

All efforts should be made to contact participants who miss scheduled study visits (unless the participant has withdrawn consent). For participants who fail to attend a study visit, and who cannot be reached by phone, a home visit will be attempted, following site-level SOPs for retention in clinical trials.

6.4 Possible poor treatment response (PPTR)

A possible poor treatment response (PPTR) evaluation by the trial Clinical Management Committee (CMC) is triggered by any one or more of the following, but not limited to:

a. Worsening signs and/or symptoms consistent with TB at or after Week 12.
b. Radiographic worsening consistent with TB at or after Week 12.
c. AFB sputum smear-positivity involving at least two separate sputa at or after Week 12.
d. At least one *Mtb* culture positive at or after Week 12.
e. The site investigator is considering retreatment (or extended treatment) with any TB therapy after the participant has completed assigned study treatment.

f. For a participant on assigned study treatment, the site investigator is considering a change in treatment for efficacy reasons This includes addition, subtraction, replacement of TB medications for any reason except changes in treatment for pregnancy, temporary drug challenge, or toxicity.

If a poor treatment response is suspected, the CMC should be contacted as outlined in the CMC SOP. Investigations to evaluate a PPTR will be conducted at the discretion of the site investigator in consultation with the CMC. Treatment decisions will be based on clinical and radiographic response, and AFB and mycobacterial culture results, using methods similar to those of S31/A5349.[81] A treatment failure visit (described in section 5.3.1.15) will be triggered by consensus agreement of the CMC, in conjunction with the site PI, for participants experiencing extension of treatment or retreatment beyond the nominal level (week 12 for Arm 1 and week 26 for Arm 2). Participants in Arm 1 who require re-treatment will receive 26 weeks of standard TB therapy. All participants in both groups who require re-treatment will remain on study. Participants in both groups with recurrent TB diagnosed prior to 60 weeks after enrollment will be treated by the study team; those who relapse after 60 weeks will be referred to the National TB Program for treatment according to standard of care.

7 ASSESSMENT OF SAFETY

7.1 Assessing and Recording Safety Parameters

7.1.1 Definitions of Adverse Events (AEs)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study regardless of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.1.2 Adverse Events Grading

All recorded AEs (defined below in 7.1.3) will be graded for severity and assessed for relationship to study drugs. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity. AEs will be assessed by the investigator using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 (with the exception of QTcF, which is graded according to Table 6 below). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the participant's usual activities of daily living.

Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

Life-threatening (Grade 4): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

7.1.3 AE collection requirements

The following AEs must be recorded on eCRFs if any of the following criteria have been met:

- All AEs that led to a change in study treatment regardless of grade
- All AEs meeting SAE definition (see below)
- All Grade ≥3 AEs
- All Grade ≥2 AEs for the following conditions:
  - Conduction abnormality/atrioventricular heart block
  - QTcF prolongation
  - Hyperpigmentation
  - Dry skin
  - Photosensitivity
  - Pruritus/itching
  - Rash
  - Hepatitis, as defined by elevations in ALT, AST, or total bilirubin

All AEs meeting recording criteria during the study period will be captured on the appropriate data collection form and eCRF, regardless of their relationship to study medication. Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology, date of resolution, seriousness and outcome. AEs will be followed through resolution. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

7.1.4 Serious Adverse Events (SAEs), Suspected Serious Adverse Reaction (SSAR), Suspected Unexpected Serious Adverse Reaction (SUSAR)

7.1.4.1 SAE

An AE or suspected adverse reaction is considered a serious adverse event (SAE) if, in the view of either the site principal investigator or CMC, it results in any of the following outcomes:

- Death
- A life-threatening adverse event (places the participant at immediate risk of death from the event as it occurred)
- Inpatient hospitalization or prolongation of existing hospitalization (with the exception of planned elective hospitalization or social admission)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of

such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

7.1.4.2 SSAR and SUSAR

Any SAE or grade 4 AE that is believed with a reasonable probability to be due to study treatment will be considered a Suspected Serious Adverse Reaction (SSAR). In making this assessment, site investigators should consider the probability of an alternative cause (for example, TB itself or some other condition preceding randomization), the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

SSARs will be reported to the trial CMC for expedited review, and an assessment made of whether the event is serious, related to study medication, or expected. SSARS will also be reported to DMID-CROMS in real time. Any SSARs that are not expected will be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR). All confirmed SUSARs and SSARs will be reported to the Chair of the DSMB and to relevant regulatory authorities, ethics committees, and investigators in accordance with regulatory requirements.

7.1.5 Type and Duration of Follow-up of Participants after Adverse Events

Recorded AEs will be assessed, and followed from initial recognition of the AE through end of the protocol defined follow-up period. SAEs will be followed up through resolution even if duration of follow-up goes beyond the protocol-defined the follow-up period. Resolution of an AE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

7.2 Reporting Procedures

7.2.1 Reporting procedures

Any SAE, SSAR, or SUSAR must be reported to the Sponsor, local IRB, DMID, DMID-CROMS and regulatory agencies on an Adverse Event Report within 48 hours of the site's awareness of the event.

For participants who die, as much information as possible on cause of death and details of the final illness will be obtained from relevant sources. All relevant follow up SAE information must be provided to the regulatory agencies within 7 days of becoming available to the study site.

The AE reporting period for this study is the entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason). After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs will be reported if the study staff become aware of the events on a passive basis.

7.3 Clinical management issues

Criteria for participant management, dose interruptions, modifications, and discontinuation of treatment are mandated only for toxicities attributable to study-provided drugs. The trial CMC must be notified within 48 hours regarding toxicities that result in a change in study treatment (including transitory or permanent discontinuation) during the study-defined treatment period. The CMC SOP lists indications for immediate stopping of study drugs, while awaiting a response from the CMC.

7.3.1 General

7.3.1.1 Grade 1 or Grade 2 toxicity

Participants who develop a Grade 1 or 2 AE or toxicity may continue study drugs without dose adjustment. Participants experiencing Grade 1 or 2 toxicities will be managed at the discretion of the site investigator. Electrolyte abnormalities should be corrected and rechecked.

7.3.1.2 Grade 3 toxicity

For any Grade 3 AE or toxicity thought to be secondary to study drugs or of unknown etiology, site investigators must discuss toxicity management with the CMC. If there is compelling evidence that the AE has NOT been caused by the study drugs, dosing may continue at the discretion of the site investigator/clinician. Except as stated below, participants who develop a Grade 3 AE or toxicity thought to be secondary to study drugs or of unknown etiology will have study drugs withheld. Investigators will discuss toxicity management with the CMC, and study drugs may be restarted sequentially, depending on the clinical situation; such decisions will be made on a case-by-case basis after consultation with the CMC. The participant should be reevaluated at least weekly until the AE returns to Grade ≤2 or until stabilized and clinically no longer in need of weekly monitoring. Participants developing Grade 3 toxicity felt to be due to study drugs that does not resolve within 14 days may need to be discontinued from the study medications and re-treated with standard treatment. They will continue to be followed on-study, off study drugs. These cases should be managed individually in conjunction with the CMC.

7.3.1.3 Grade 4 Toxicity

For any Grade 4 AE or toxicity thought to be secondary to study drugs or of unknown etiology, site investigators will discuss toxicity management with the CMC. For a Grade 4 event thought to be secondary to study drugs (decided in conjunction with the CMC), the participant may need to be hospitalized and will be discontinued permanently from study TB medications. The participant will be re-treated with standard treatment and will continue to be followed on study.

7.3.2 Specific Conditions

7.3.2.1 QTcF Prolongation

Patients who receive BDQ, CFZ, and DLM have the potential of prolongation of the QTcF interval. Grading is based on the average of triplicate ECGs at each visit, as per definitions in Table 6 below:

Table 6. QTcF Prolongation Grading.

Grade 1	Grade 2	Grade 3	Grade 4
(1) Absolute QTcF >480 and ≤500 ms and QTcF change from baseline >0 ms and ≤30 ms; or (2) Absolute QTcF ≤480 ms and QTcF change from baseline >30 and ≤60 ms	(1) Absolute QTcF >480 ms and ≤500 ms and QTcF change from baseline >30 ms and ≤ 60 ms; or (2) Absolute QTcF ≤480 and QTcF change from baseline >60 ms	(1) Absolute QTcF >500 ms; or (2) Absolute QTcF >480 and QTcF change from baseline >60 ms	Life-threatening consequence, e.g., torsades de pointes or other associated serious ventricular dysrhythmia

If Grade 2 QTcF prolongation develops during the course of study treatment, the participant will be monitored more closely, with once weekly ECG testing, and correction of electrolytes where necessary. If Grade 3 QTcF prolongation occurs, experimental therapy will be discontinued and the participant will be carefully monitored until the abnormality returns to Grade ≤2. Electrolytes will be checked and repleted where necessary. Repeat ECG following repletion of electrolytes will be performed within 3 days, and if QTcF reading is a Grade ≤2, study medication may be restarted, at the discretion of the investigator and CMC. If Grade 3 finding remains, experimental therapy will be permanently discontinued.

For a Grade 4 event, the participant will be referred for hospitalization and discontinued permanently from study TB medications. The participant will be re-treated with standard treatment and will continue to be followed on study. All Grade 3 or higher QT events should be discussed with the CMC.

7.3.2.2 ALT or Total Bilirubin Elevation

Many antituberculosis drugs, including the experimental drugs and components of SOC can cause alterations in liver chemistry tests. Participants entering this trial will have active TB and elevation in liver function tests is expected. Concomitant illnesses, including HIV infection, and other medications, such as cotrimoxazole and antiretrovirals, may also alter these laboratory parameters. Therefore, changes in liver chemistry tests (ALT, AST, bilirubin) should be evaluated within the clinical context of the abnormalities. Liver chemistry tests will be checked regularly for all study participants, as per the schedule of events.

For Grade 1 or Grade 2 elevations, study drugs should be continued and repeat liver chemistries (ALT, AST, total bilirubin) at 1 week. Subsequent testing should be conducted at regular intervals at the investigator's discretion until resolution to ≤ULN or to baseline if abnormal at entry.

All participants who have new Grade ≥3 elevation of ALT should be evaluated for alcohol-induced hepatitis, non-study medication-related toxicity, viral hepatitis, and immune reconstitution inflammatory syndrome. The CMC and routine care clinicians should be consulted regarding management of study medications if any of these conditions is suspected. For participants who develop asymptomatic or symptomatic Grade 3 elevations during study treatment, and the elevations are not attributed to another cause, study-provided TB drugs should be discontinued for up to 2 weeks. Non-study-supplied ART should be continued at the discretion of routine care clinicians. Liver function and chemistry tests should be repeated weekly and study-provided TB drugs held until levels and symptoms are Grade ≤2, at which time therapy may be reintroduced. After consultation with the CMC, if an alternative cause is documented and the ALT or total bilirubin takes longer than 14 days to reach Grade ≤2 toxicity, study-provided drugs may be restarted.

If Grade 3 toxicity recurs after re-introduction of study-provided drugs and SOC (and ART, if applicable), or if Grade 3 toxicity does not resolve within 14 days, or if any Grade 4 toxicity develops, the participant will have study-provided drugs permanently discontinued and will be re-treated with standard treatment and will continue to be followed on study.

All TB treatment should be interrupted if clinically significant hepatitis occurs, defined as Grade ≥2 ALT or AST in association with:

- Elevated total bilirubin >2xULN, and/or
- Signs or symptoms of clinical hepatitis (e.g., fatigue, nausea, vomiting, right upper quadrant pain, jaundice)

For participants who develop clinically significant hepatitis during study treatment, liver function tests should be repeated at least weekly and study-provided drugs

held until levels and symptoms are Grade ≤2, at which time therapy may be reintroduced in consultation with the CMC. If an alternative cause is documented and the ALT or total bilirubin takes longer than 14 days to reach Grade ≤2, consideration may be given to resuming study drugs, with approval from the CMC.

7.3.2.3 Allergic Reaction

Participants may continue study drugs for Grade 1 or Grade 2 allergic reactions at the discretion of the study investigator. The participant should be advised to contact the study team immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to a study drug should permanently discontinue that study drug. Participants should be treated as clinically appropriate and followed until resolution of the AE. These participants will remain on study until the completion of study follow-up.

7.3.2.4 Severe Rash/Cutaneous Reaction

Moderate to severe rash potentially related to drug hypersensitivity may occur with any of the study provided TB drugs as well as other drugs participants may be taking. Participants with a Grade 1 rash may continue study drugs at the study investigator's discretion. Investigators are advised to contact the CMC immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops. Participants may continue study drugs for an isolated Grade 2 rash. However, study drugs (and all other concurrent medications suspected in the investigator's causality assessment) should be permanently discontinued for any Grade ≥3 rash or for any Grade ≥2 rash that is associated with any of the following:

- Increase in ALT
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Fever, generalized malaise or fatigue
- Muscle or joint aches
- Blisters
- Oral lesions
- Eye inflammation
- Facial swelling
- Swelling of the eyes, lips, mouth
- Breathing difficulty
- Signs and symptoms of liver abnormalities

If the etiology of the rash can be definitely diagnosed as being unrelated to study drugs and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

Participants taken off study drug for rash will be re-treated with standard treatment and will continue to be followed on study.

7.3.2.5 Abdominal Pain, Nausea, and/or Vomiting

Although not uncommon, nausea following initiation of therapy with experimental therapy, standard TB medications, and/or antiretroviral medications is usually mild and subsides or resolves during treatment. Steps in the management of nausea include taking the medication with food and administration of antiemetic.

Participants with Grade ≥3 vomiting or abdominal pain should have their hydration status assessed and be referred to appropriate local medical care for monitoring and volume resuscitation if clinically indicated depending on site- specific standard practices. If Grade 3 or Grade 4 abdominal pain, nausea and/or vomiting occurs, if there is compelling evidence that these have NOT been caused by study-provided drugs, dosing may continue and supportive care given. If, after discussion with the CMC, the site investigator determines that Grade 3 or Grade 4 abdominal pain, nausea and/or vomiting is possibly or probably related to study-provided drugs then study-provided drugs may be temporarily held for up to 14 days until these symptoms return to Grade ≤2. If symptoms do not reach Grade ≤2 within 14 days or if Grade 3 or Grade 4 symptoms occur after reintroduction, then study-provided drugs should be permanently discontinued and the participant will be re-treated with standard treatment. These participants will continue to be followed on study.

7.3.2.6 Arthritis/Arthralgia

Arthritis and arthralgia are common symptoms experienced by participants on pyrazinamide. If a participant develops Grade ≤3 arthritis or arthralgia during the course of the study, the participant will continue on study drugs and be treated according to local standard practices. If the participant develops Grade 4 arthritis or arthralgia, pyrazinamide will be held for up to 14 days until toxicity resolves to Grade ≤2. If toxicity does not resolve to Grade ≤2 within 14 days, the participant will be discontinued from study medications, re-treated with standard treatment, and followed on study, off study drugs. If toxicity resolves to Grade <2 within 14 days but Grade 4 arthritis or arthralgia occur after reintroduction of pyrazinamide, pyrazinamide will be permanently stopped.

7.4 Safety Oversight (CMC, DSMB)

7.4.1 Clinical Management Committee

The CMC will be represented by clinicians embedded within the Trial Management Group structure plus independent TB specialists. The function of the CMC is to respond to site queries relating to protocol and SOP interpretation, plus individual clinical management issues including possible poor treatment response and adverse drug reactions. The activities of the CMC are described in an SOP.

7.4.2 Data and Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group with expertise to interpret data from this study and will monitor participant safety. The DSMB members will be separate and independent of study personnel participating in this study and should not have scientific, financial or other conflict of interest related to this study. The DSMB must consist of at least three voting members, including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise.

The DSMB will operate under the rules of a charter that defines the data elements to be assessed and the procedures for data reviews and will be written at the organizational meeting of the DSMB. Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and reportable AEs. The DSMB will review SAEs on a regular basis and *ad hoc* during this trial. As defined in the charter, the DSMB will review data at specified times during the course of the study for participant and overall study progress,and will conduct *ad hoc* reviews as appropriate when a DSMB review trigger is met or for immediate concerns regarding observations during this study.

8 HUMAN PARTICIPANTS PROTECTION

8.1 Institutional Review Board/Independent Ethics Committee

Each site principal investigator will obtain IRB approval for this protocol to be conducted at his/her research site(s) and send supporting documentation to the Sponsor before initiating recruitment of participants. Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and follow-up of participants and may cease if annual review is no longer required by applicable regulations and the IRB/IEC. The investigator will notify the IRB/IEC of deviations from the protocol and reportable AEs, as applicable to the IRB/IEC policy.

8.2 Informed Consent

8.2.1 Informed Consent Process

Before any study procedures are performed, informed consent will be obtained and documented. Participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written or electronic consent form. A copy of the consent form will be given to the participant, and this fact will be documented in the participant's record. The consent forms will be stored securely, separately from other de-identified trial documents. Participants who are illiterate can be consented and enrolled in the trial if they are otherwise willing and eligible and if independent consent is ensured. If the participant is not able to read, an impartial literate witness who speaks the language of the participant must be present during the entire informed consent discussion with the participant. For those patients who cannot sign their name, a fingerprint will be accepted.

8.2.2 Consent for Future Use of Stored Specimens and Data

Participants will be asked for permission to store clinical samples, with a separate section for human genetic analysis (South Africa only), to identify potential biomarkers of tuberculosis treatment response, as described above. These specimens will be stored coded indefinitely. Specimens may be shared with other investigators designated by the study PIs. The information provided to a recipient will not contain direct identifiable information, and the samples will only be identified by a study specific participant identification number.

8.3 Exclusion of Women, Minorities, and Children (Special Populations)

No one will be excluded from study participation based on sex/gender, racial or ethnic group. Pregnant and lactating women will not be included in the study as agents in the experimental regimen (BDQ, CFZ and DLM) are not currently advised due to a lack of evidence on safety, efficacy and proper dosing in these groups. All women in whom a new pregnancy is discovered at

enrollment, or during the trial will be referred for obstetric care, and pregnancy outcomes ascertained.

Children will be excluded from this trial for three main reasons: 1) patients younger than 18 years often attend different clinical services to the clinics that we will be focusing on; 2) TB treatment guidelines and dosing vary between adults and children; and 3) consent cannot be provided by individuals younger than 18 years for participation in medical research in South Africa. According to the South African National Health Act of 2003, if a study is categorised as therapeutic (this applies to our study), the research may only be conducted if it is in the best interests of the minor; with the consent of the parent or guardian of the child; and if the minor is capable of understanding, with the consent of the minor. If this Phase IIc trial demonstrates superiority for the experimental regimen, this will provide strong rationale to include children, particularly adolescents, in subsequent trials with clinical endpoints. Additionally, pharmacokinetic analyses and clinical trial simulations will inform dosing for patients in lower weight bands in future trials.

8.4 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site or captured on databases will be identified by coded number only to maintain participant confidentiality. All records will be kept locked and in secure databases. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the Sponsor, IRBs, or regulatory authorities as part of their duties, or the industry supporter(s) or designee.

8.5 Costs, Participant Compensation, and Research Related Injuries

There is no cost to participants for the research tests, procedures, and study product while taking part in this trial. Participants will be compensated for their participation in accordance with the local IRB's policies and procedures. Immediate medical treatment may be provided by trial personnel if needed, with referral to appropriate routine care.

9 STATISTICAL CONSIDERATIONS

9.1 Primary Hypothesis

Null hypothesis: No difference in time to culture conversion by 8 weeks between the experimental arm (Arm 1: BCZD) and standard therapy (Arm 2: RHZE).

Alternate hypothesis: The 12-week experimental regimen (Arm 1: BCZD) will demonstrate superior microbiologic efficacy (time to liquid culture conversion during the first 8 weeks of treatment) relative to standard therapy (Arm 2: RHZE).

9.2 Definitions of composite TB outcome status (key secondary and exploratory efficacy outcomes)

9.2.1 Favorable Outcome *(*any one of the following scenarios)

- Participants with liquid culture negative status at week 60
- Participants who are unable to produce a sputum specimen at week 60 and are without signs or symptoms of ongoing active TB
- Participants who produce a sputum specimen that is contaminated in two liquid cultures at week 60 but who are without symptoms/signs of ongoing active TB

The composite clinical outcome will be determined separately at week 60. For any of the above to be considered favorable, participants must not already have been considered unfavorable or unevaluable, as defined below.

9.2.2 Unfavorable Outcome (any one of the following scenarios)

- Absence of cure
  A participant will be considered to have absence of bacteriological cure if a sputum sample obtained after end of treatment (week 12 for Arm 1, week 26 for Arm 2), that is culture-positive in liquid or solid media for an *Mtb* strain genotypically matched with the initial isolate. A second sputum sample, obtained on a separate sputum sample following the first sputum collection, is required to confirm absence of bacteriological cure. A second confirmatory sample is required as a single positive sputum culture in isolation will not be considered absence of bacteriological cure.

- Death
  Participants who die from any cause while on study except from violent or accidental cause (e.g., road traffic accident).

- Last available culture positive

Participants who had a positive culture for *Mtb* when last seen, whether confirmed by a second sample or not.

- Treatment extension
  Participants experiencing extension of treatment beyond the nominal level (week 12 for Arm 1 and week 26 for Arm 2). These cases should be managed individually in conjunction with and after having notified the CMC. Extension of treatment to make up missed doses will not count as unfavorable.

9.2.3 Unevaluable Outcome

- Participants lost to follow-up during treatment or follow-up with their last culture being negative for *Mtb*.
- Participants who die from violent or accidental death.
- Participants with recurrent TB due to a new strain of *Mtb* confirmed by whole genome sequencing.
- Women who become pregnant during their assigned active treatment and stop their assigned treatment.

9.3 Sample Size Considerations

This trial is powered for the primary outcome measure of comparing time to liquid culture conversion through 8 weeks in Arm 1 (experimental) versus Arm 2 (control). Based on a systematic review of published historical Phase 2/3 trial data (Figure 5, Forest Plot), we estimate that 60% of Arm 2 participants will experience culture conversion within 8 weeks. We assume the true underlying hazard ratio to be 1.8 for Arm 1 vs. Arm 2, corresponding with a 35% relative increase in culture conversion over Arm 2. With a one-sided alpha level of 0.05 and 1:1 allocation to Arm 1: Arm 2, we would require 142 participants to have 90% power to reject the null hypothesis of no difference in time to culture conversion by 8 weeks between the two arms. To account for possible late exclusions, withdrawals, and missing culture results, we include a 10% inflation resulting in a total required sample size of about 156 participants. Sample size calculations were performed using PASS software version 15.0.4.

Table 7. Required Sample Size Estimates

Effect Size			Required Sample Size for 90% Power		
Proportion Culture Conversion at 8 weeks in Standard Regimen Arm (Arm 2)	Proportion Culture Conversion at 8 weeks in BDQ-CFZ-PZA Arm (Arm 1)	Hazard Ratio	Required # Participants for Standard Regimen Arm	Required # Participants for BDQ-CFZ-PZA Arm	Total Required Sample Size
0.65	0.83	1.7	83	83	166
0.65	0.85	1.8	67	67	134
0.65	0.86	1.9	56	56	112

0.60	0.79	1.7	88	88	176
0.60	0.81	1.8	71	71	142
0.60	0.82	1.9	59	59	118
0.55	0.74	1.7	94	94	188
0.55	0.76	1.8	76	76	152
0.55	0.78	1.9	63	63	126

This is a phase IIc trial with a microbiological primary endpoint, and not a definitive trial. The 8-week culture conversion rate that will translate into clinical efficacy is unknown. Demonstrating a HR or 1.8 for the primary outcome measure of time to culture conversion by 8-weeks will strongly support microbiological superiority of the experimental regimen, and the phase 2c design will enable collection of clinical outcomes data, thus informing a follow-on phase 3 trial. The risk of assuming a larger effect size is that a smaller true effect, possibly leading to relapse-free cure, may be missed resulting in abandoning a potentially effective regimen (Type 2 error), particularly because long elimination phase of BDQ and CFZ may provide ongoing efficacy after treatment discontinuation. The risk of powering for a smaller effect size is increased costs from a larger sample size, plus it is likely that high 8-week culture conversion rates (> 80%, as assumed in our estimates) will be needed for a 12-week regimen to be effective. Furthermore, a HR of 1.8 was selected in the MAMS-TB trial as a criterion to indicate potential for treatment shortening[55] providing precedent for our approach. Our assumed effect size is substantially higher than a HR of 1.4, which was associated with a successful 4-month treatment shortening rifapentine-moxifloxacin regimen in the Study 31/A5349 trial.[7]

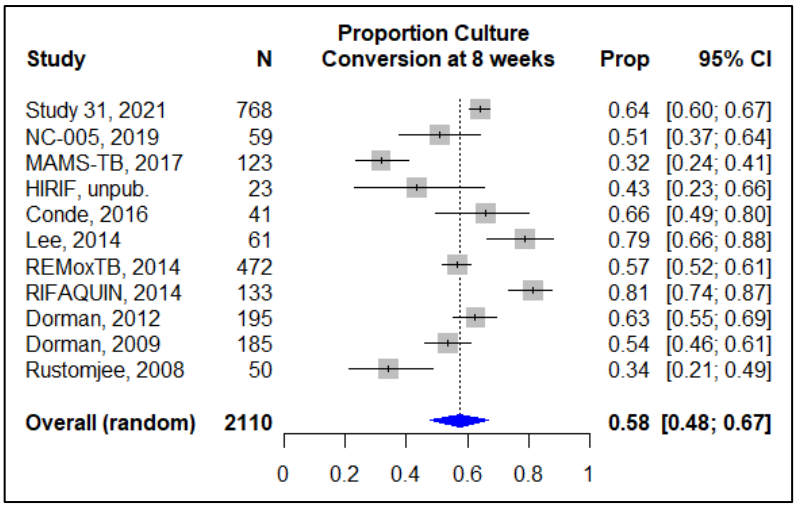
Table 8. Liquid Culture Conversion at 8 weeks in RHZE Control Groups in Historical Phase 2 and Phase 3 Trials*

Study or First Author and Year of Publication	Smear positive at baseline	Number evaluated	Number with Liquid Culture Conversion at 8 Weeks	Proportion with Liquid Culture Conversion at 8 Weeks (%)
Phase 3 trials				
Study 31	Smear-positive or semiquantitative result of medium or high by Xpert MTB/RIF	768	491	64
REMoxTB Trial, 2014[82]δ	Positive	472	267	57
RIFAQUIN, 2014[83]*δ	Positive	133	108	81*
Phase 2 trials				
Rustomjee et al, 2008[84]δδ	Positive	50	17	36[#]
MAMS-TB, 2017[85]δ	Positive	123	39	32
HIRIF[86], 2017 (confidential, unpublished data)***δ	Positive	23	10[^]	43
NC-005, 2019[53]δ	Positive	59	30	51
Dorman et al, 2009[87]δδ	Positive	185	99	54
Dorman et al, 2012[88]δδ	Positive	195	122	63

Conde et al, 2016[89]δ	Positive	41	27	66
Retrospective clinical cohort from Korea– Lee et al PLOS One 2014	Positive	61	48	79
Total		**2110**	**1269**	**60%**

*In RIFAQUIN, MGIT was used for cultures from Botswana, South Africa, and Zambia only; +/- 2-week window allowed for 2-month cultures; **OFLUTUB[90] was excluded because solid cultures were conducted; ***Confidential data from HIRIF study included 6 and 8 week cultures; δTreatment provided daily; δδ Treatment provided 5 or 6 days/week. # patients had severe pulmonary disease, almost all with cavitation, 59% HIV+. ^ Week 6; exclusion of 2 patients with contaminated cultures

Figure 5. Meta-analysis of 8-week culture conversion proportions from published trials.



9.3.1 Power for Secondary Safety Outcome Measure

For the secondary safety outcome, we will compare proportions of participants with any Grade 3 or higher AE between arms. Table 9 gives the power we would have to detect that Arm 1 is inferior to Arm 2 assuming a two-sided type 1 error of 0.10, 10% probability of developing an AE in the SOC arm, and varying probabilities (15-30%) of developing an AE in experimental arm. The 90% confidence interval width (Wilson score test with continuity correction) is also provided for the comparison.

Table 9. Secondary Safety Outcome Power and Precision

Total Sample Size	Two-sided type 1 error (alpha)	Arm 1 proportion with ≥ Grade 3 AE	Arm 2 proportion with ≥ Grade 3 AE	Power	Precision (90% CI Width)
142	0.10	0.15	0.10	0.16	0.207
142	0.10	0.20	0.10	0.42	0.218
142	0.10	0.25	0.10	0.69	0.227
142	0.10	0.30	0.10	0.88	0.234

9.3.2 Power for Secondary Efficacy Outcome Measure

For the secondary composite clinical/bacterial efficacy outcome, we assume a favorable outcome proportion of 84-92% in the control arm by week 60. This estimate is based on the modified intent to treat control arms of the RIFAQUIN and REMox trials.

For the proportion with favorable composite outcome at 60 and using an unpooled Z-test with one-sided alpha of 0.05 and sample sizes of 71 in Arm 1 and 71 in Arm 2, the power for a range of non-inferiority margins and favorable outcome proportions from 84% to 92% is given in Table 10. Note that a margin of 6-7% (with a one-sided alpha of 0.025) is commonly used in Phase III drug-sensitive TB treatment shortening trials, but we would have little power on this secondary endpoint to show non-inferiority based on that margin. For this reason, we will not be making a formal comparison with a pre-specified non-inferiority margin, and will solely provide the one-sided 95% confidence interval (Wilson Score test with continuity correction) for the difference in proportions between arms.

Table 10. Secondary Efficacy Outcome Power

Total Sample Size	Proportion Favorable in each arm	Non-inferiority Margin	Power	One-sided 95% Confidence interval lower bound
142	0.84	0.08	0.365	0.112
142	0.84	0.10	0.492	
142	0.84	0.12	0.620	
142	0.88	0.08	0.429	0.102
142	0.88	0.10	0.575	
142	0.88	0.12	0.710	
142	0.92	0.08	0.545	0.09
142	0.92	0.10	0.709	
142	0.92	0.12	0.839	

9.4 Treatment Assignment Procedures

9.4.1 Randomization Procedures

Participant identification numbers (PID), assigned at the screening visit, will be used throughout the study. Randomization will occur at the Enrolment visit after reviewing results from screening procedures and final eligibility confirmation by a study investigator. Eligible participants will be randomly allocated to each study arm in a 1:1 ratio (78 per arm, total = 156) using stratified random permuted blocks to ensure balance of key prognostic variables across arms and balanced participant numbers per arm over time. Enrollment of persons with HIV will be limited to no more than 20% (n = 32) of the total study population. The initial 25% of the trial population will include only participants with

mild/moderate disease, as defined by a sputum Xpert Ct value > 17 and absence of extensive involvement on CXR. Stratification will be by HIV status and presence of lung cavitation. Cavitation is defined as a gas-containing lucent space of at least 1cm in diameter within the lung parenchyma surrounded by an infiltrate or fibrotic wall greater than 1mm thick seen on CXR, as in Study 31/A5349. CXRs will be interpreted at the site level. The trial will use a centralized, web-based randomization program (with telephonic backup in case of internet connectivity problems). A randomization list will be generated by the trial data manager who will have no direct contact with trial participants or involvement in eligibility assessment. This is an open-label trial, therefore treatment allocation will not be concealed, but access to the randomization list is restricted to the authorized trial data manager.

9.4.2 Masking Procedures

This is an open-label trial; no masking will occur.

9.5 Analysis Plan

In accordance with ICH E9 (R1), the statistical analysis of this clinical trial is aligned to the primary and secondary estimands, which will answer the pre-specified trial objectives. A separate primary SAP document fully details the estimands for each primary and secondary trial objective.

9.5.1 Primary and Key Secondary Estimands

9.5.1.1 **Primary efficacy estimand:** Time to stable liquid culture conversion through 8 weeks of follow-up.

The analysis set will include all participants who were randomized to study treatment and who are not late exclusions (participants whose screening, entry, and first post-entry visit sputum cultures all fail to grow *Mtb* complex or whose molecular or drug susceptibility test results demonstrate resistance to INH or RIF after enrollment). We will measure time to stable liquid culture conversion based on sputum samples taken at serial collections up to 10 weeks after treatment initiation. The time of stable culture conversion will be the time of the sampling date of the first of two culture negative sputum samples in liquid media (MGIT) without an intervening positive culture. The inability to produce sputum together with no signs or symptoms of active TB at a given visit will be considered a negative sputum culture.

The primary population-level summary measure will be the HR of culture conversion through 8 weeks of follow-up estimated by a Cox-proportional hazards model with HIV status and presence of advanced disease as stratification factors. We will report the HR and corresponding two-sided 95% confidence interval

considering BCZD to be superior to standard treatment if the lower confidence bound is greater than 0. As a supplemental measure of treatment effect, we will estimate the difference in restricted mean survival times for a time horizon of 8 weeks.

9.5.1.2 **Key Secondary Estimand (Safety):** Probability of having at least one grade 3 or higher adverse event through 60 weeks including any occurrence that is new in onset or aggravated at least a one-grade from baseline.

The analysis set will include all participants who started their assigned study treatment. We will measure the occurrence of a Grade 3 or higher adverse event through 60 weeks that is new in onset or aggravated in severity of frequency from the baseline condition.

The population summary measure will be the probability of having at least one Grade 3 or higher AE including any occurrence that is new in onset or aggravated at least one-grade increase from baseline at any time during the 60 weeks after treatment initiation. We will compare the cumulative probability at any time during the 60-week study period between Arm 1 and Arm 2 using the Kaplan-Meier estimator at week 60. We will present the point estimate and 90% two-sided confidence intervals for the difference in cumulative probabilities.

9.5.1.3 **Key Secondary Estimand (Favorable composite outcome):** Difference in proportion with favorable outcomes 60 weeks after initiation of TB therapy.

The analysis set will include all participants who started their assigned study treatment and are not late exclusions or unevaluable (per definition in Section 9.2). We will measure whether the favorable outcome is achieved 60 weeks after initiation of TB therapy. Favorable outcome is defined in Section 9.2.

The population summary measure will be the difference in cumulative probability of having a favorable outcome at 60 weeks after TB therapy initiation. We will estimate the difference in cumulative proportion of participants at week 60 together with 90% and 95% two-sided confidence intervals. We will use the Kaplan-Meier estimator and Greenwood's estimate for the variance.

9.5.2 Analysis of Other Secondary and Exploratory Objectives

These will be detailed in a separate SAP.

9.6 Planned Interim Monitoring and Analyses

The study will be reviewed at least annually by a Data Safety Monitoring Board on a schedule outlined in the DSMB charter. For all reviews, the DSMB will be provided detailed information by randomization arm on safety, tolerability, and administrative aspects (including accrual, retention, and compliance with study requirements). In addition to routine monitoring of participant safety and study conduct, we will carefully monitor for hepatitis, QT prolongation, and TB recurrence. Details of these analyses and triggers for DSMB review are described in the DSMB charter.

9.6.1 Early Recurrence Monitoring

TB recurrence monitoring will begin after the first Arm 1 participant completes 12 weeks of treatment and continue until the end of the study. Recurrence will capture confirmed relapses and reinfections. Since recurrence data on SOC will be lagging behind the experimental arm, recurrence data in experimental arms will be compared with historical SOC data from REMox, OFLOTUB, RIFAQUIN, Study 31 (A5349) trials, and current SOC data within PRESCIENT as it becomes available. Two-sided 95% confidence bands for the cumulative probability of recurrence over time will be generated monthly for the study team and ahead of each DSMB review. If the lower 95% confidence bound for the cumulative probability exceeds 3% at any time, this will trigger a DSMB review. There will be no adjustment to the confidence bands for multiple looks.

10 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the Sponsor, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Each participating site is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. Data and safety monitoring will include regular DSMB reviews, a data management, clinical quality management plan, and scheduled visits by an independent monitor that will be audited by the sponsor and local regulatory authorities.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Management Responsibilities

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Copies of the electronic CRF (eCRF) will be available for use as source data collection forms and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source data collection forms should be consistent or the discrepancies should be explained.

12.2 Biostatistician Responsibilities

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site principal investigator. During the study, the site principal investigator must maintain complete and accurate documentation for the study. The Harvard School of Public Health will be responsible for data management, quality review, analysis, and reporting of the study data.

12.3 Data Capture Methods

Clinical data will be collected on data collection forms by study personnel then entered into the trial database, or directly entered into the database. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

12.4 Study Records Retention

All essential documents pertaining to the trial will be retained for not less than 10 years.

13 CLINICAL MONITORING

Site monitoring is conducted to ensure that the human participants' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures. An external clinical trial monitor will conduct site-monitoring visits as detailed in the clinical monitoring plan. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol and GCP compliance. Monitors will have access to each participating site, study personnel, and all study documentation according to the approved site monitoring plan. Study monitors will meet with site principal investigators to discuss any problems and actions to be taken, and will document site visit findings and discussions.

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APPENDIX A: CONCOMITANT MEDICATIONS

Disallowed drugs

The following medications are disallowed, for each specific anti-tuberculosis drug, during the treatment and up to 1 month after the end of treatment:

Bedaquiline

1. Moderate and strong CYP3A4 inhibitors:
   - Ritonavir
   - Lopinavir
   - Atazanavir
   - Darunavir
   - Indinavir
   - Nelfinavir
   - Saquinavir
   - Tipranavir
   - Ketoconazole
   - Voriconazole
   - Itraconazole
   - Fluconazole
   - Telithromycin
   - Clarithromycin
   - Erythromycin
   - Fidaxomicin
   - Spiramycin
   - Boceprevir
   - Telaprevir

2. Moderate and strong CYP3A4 inducers:
   - Efavirenz
   - Phenytoin
   - Carbamazepine
   - Phenobarbital
   - St. John's wort
   - Rifampicin
   - Rifabutin
   - Rifapentine

3. Amiodarone

Delamanid

1. Strong CYP3A4 inducers:
   - Phenytoin
   - Carbamazepine
   - Phenobarbital
   - St. John's wort
   - Rifampicin
   - Rifabutin
   - Rifapentine

2. Amiodarone

There are no additional absolute contraindications on medications delivered concomitantly with clofazimine or pyrazinamide.

For concomitant medications that have the potential to prolong the QT interval or are associated with torsades de pointes, clinical investigators will be instructed in the study operating procedures to avoid the drug in regimens with other QT prolonging drug(s) and if not possible to use with caution. The list of QT-prolonging drugs can be found by consulting CredibleMeds (https://www.crediblemeds.org).