Statistical Analysis Plan (Revised): Early Termination of Gates MRI-TBD06-201

Trial Title:	A Phase 2b/c, Multi-Arm, 2-Stage, Duration Randomized Trial of the Efficacy and Safety of Two to Four Months Treatment with Regimens Containing Bedaquiline, OPC-167832, and Sutezolid, Plus Either Pretomanid or Delamanid, in Adults with Pulmonary Tuberculosis
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Trial Phase:	2b/c
Sponsor:	Bill & Melinda Gates Medical Research Institute (Gates MRI) 245 Main Street Cambridge, MA 02142
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2 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SIGNATURE PAGE

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

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2HRZE/4HR	2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) followed by 4 months of isoniazid (H) and rifampicin (R)
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
AUC	area under the concentration-time curve
ART	antiretroviral treatment
BMI	body mass index
CFB	change from baseline
CI	confidence interval
cm	centimeter
CMH	Cochran-Mantel-Haenszel
CXR	chest X-ray
DAIDs	Division of Allergy and Infectious Diseases
DBOS	delamanid + bedaquiline + OPC-167832 + sutezolid
DBP	diastolic blood pressure
DDI	drug-drug interaction(s)
DILI	drug-induced liver injury
DOT	directly observed therapy
DS	drug-sensitive
ECG	electrocardiogram
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
ESAP	exploratory statistical analysis plan
FDC	fixed dose combination
Gates MRI	Gates Medical Research Institute
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
HR	75 mg of isoniazid and 150 mg of rifampicin
HR	heart rate

Abbreviation	Definition
HRZE	75 mg of isoniazid, 150 mg of rifampicin, 400 mg of pyrazinamide, and 275 mg of ethambutol
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
INH	isoniazid
INR	international normalized ratio
ITT	intent-to-treat
kg	kilogram
kg/m^2	kilogram per meter-squared
KM	Kaplan-Meier
[redacted]	[redacted]
logMAR	logarithm of the minimum angle resolution
LPA	Line Probe Assay
MedDRA	Medical Dictionary for Regulatory Activities
MGIT	Mycobacteria Growth Indicator Tube
MDR	multidrug resistant
mITT	modified ITT
Mtb	*Mycobacterium tuberculosis*
MUAC	mid-upper arm circumference
NTM	nontuberculous mycobacteria
OD	right eye
OS	left eye
PBOS	pretomanid + bedaquiline + OPC-167832 + sutezolid
PD	protocol deviation
PK	pharmacokinetic(s)
PP	per protocol
PP75	PP population with 75% treatment adherence
PP95	PP population with 95% treatment adherence
PR	interval from the P wave (atrial contraction or depolarization) to the onset of the Q wave in the measurement of electrical activity of the myocardium
PT	preferred term
QD	once daily
QTcF	corrected QT interval by Fridericia
RIF	rifampin
RR	respiratory rate

Abbreviation	Definition
rRNA	ribosomal ribonucleic acid
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCC	sputum culture conversion
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	standard of care
SOC	system organ class
STrAW	Stop Treatment and Watch
TB	tuberculosis
TEAE	treatment-emergent AE
TTD	time to detection
ULN	upper limit of normal
VOT	video observed therapy

4 INTRODUCTION

Although steady progress has been made over the past 2 decades in controlling the global tuberculosis (TB) pandemic and reducing annual incidence rates and deaths, there remains an urgent need for the development of new potent anti-TB agents and combination regimens with low toxicity that are effective against all *Mycobacterium tuberculosis* (Mtb) strains, can greatly reduce the duration required for treatment, and decrease the need for drug susceptibility testing before treatment initiation.

Introduced more than 40 years ago, the current recommended standard of care (SOC) for treating adults with drug-sensitive (DS) TB consists of an intensive phase of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by a continuation phase of 4 months of isoniazid and rifampicin (2HRZE/4HR). The duration and complexity of 2HRZE/4HR and its side effects frequently result in nonadherence leading to suboptimal response (with treatment failure and relapse) and emergence of resistance, including multidrug resistant (MDR) TB resistant to at least isoniazid and rifampicin. The treatment increases in complexity and duration for patients infected with rifampicin-resistant (RR)/MDR Mtb strains. In addition, drug-drug interactions caused by rifampicin's potent induction of cytochrome P450 enzymes can present challenges, particularly for women on hormonal contraception and HIV co-infected patients taking certain antiretrovirals.

Gates Medical Research Institute (Gates MRI) plans to investigate the following two proposed regimens in Stage 1 of the Phase 2 clinical trial, Gates MRI-TBD06-201:

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

Bedaquiline, delamanid, and pretomanid are approved drugs for the treatment of drug-resistant forms of TB in combination with other anti-TB agents, while OPC-167832 and sutezolid are investigational compounds in Phase 2 clinical development. These novel oral anti-TB drug regimens administered once daily have the potential to substantially shorten the treatment for all forms of pulmonary TB regardless of the resistance profile (ie, "pan-TB" regimens). If at least one of these regimens shows treatment shortening potential to 4 months with an acceptable safety profile in Stage 1, then proceeding to Stage 2 of the trial to further evaluate treatment shortening potential across a range of treatment durations from 2 to 4 months will be considered.

The purpose of this SAP is to describe the framework for the reporting, summarization, and statistical analysis methodology to address the primary and secondary objectives in Stage 1 of this trial. The original SAP was based on Protocol Gates MRI-TBD06-201 Version 3.0 dated 06 February 2024. The current version of the SAP includes revisions resulting from the early termination of the trial during Stage 1. A separate exploratory SAP may address some of the exploratory objectives of this trial, as noted in Section 8.3.

The statistical principles applied in the design and planned analyses of this study are consistent with the International Conference on Harmonisation (ICH) guidelines E9 (Statistical Principles for Clinical Trials).

5 EARLY TRIAL TERMINATION

Emerging efficacy data led to an ad hoc independent data monitoring committee (IDMC) meeting on 11 July 2024. Gates MRI provided interim microbiology results from a subset of Stage 1 participants in a 27 June 2024 data extraction. The results included participant-level longitudinal culture results, the proportion of participants with sputum culture conversion at Week 9, Week 15, and End of Treatment, and the proportion of participants with unfavorable outcome at End of Treatment and through 12 months post-randomization. Gates MRI provided the following sponsor position to the IDMC:

> "Based on the key observations noted from present trial data, the Sponsor concludes we no longer have equipoise in Stage 2 given the strong evidence in Stage 1 showing lack of efficacy for a ≤ 3-month regimen. The risk of harm due to lack of efficacy appears to outweigh the potential benefit in both investigational arms. Therefore, the Sponsor proposes to stop enrollment and offer DBOS/PBOS participants currently on study treatment the option to switch to HRZE."

The IDMC agreed with the sponsor position, and enrollment was halted.

On 12 August 2024, another IDMC meeting occurred to support the review of both safety and efficacy based on approximately two-thirds enrollment completion, as specified in the IDMC charter. The IDMC provided the following statements and recommendations:

1. The IDMC agrees with the Sponsor's termination of enrollment.
2. After careful review of the safety data, the IDMC agrees that there are no new safety concerns with the investigational regimens.
3. Given the high rates of late culture conversion and recurrence, the IDMC strongly recommends that subjects who received an investigational regimen and have not been started on a standard of care regimen, should be followed for 6 months from the end of treatment instead of 3 months.
4. The IDMC also recommends that the sponsor consider following all participants for 6 months after completion of therapy as there are likely important lessons to be learned by assessing final treatment outcomes.

Based on the IDMC's recommendation, Gates MRI communicated the following participant management plan to the trial investigators:

1. Refer participants actively receiving DBOS or PBOS investigational regimens for initiation of 6-month HRZE treatment at their local TB facility.
2. Refer participants actively receiving HRZE standard-of-care study regimen to their local TB facility for continuation of their treatment.
3. Participants who have completed DBOS, PBOS, or HRZE study treatment by 26 July 2024: Continue to follow these participants according to the protocol, visit schedule, and schedule of activities and assessments per Protocol Section 1.7, Table 3. These participants will be followed through February 2025, except for

participants completing their Month 12 Visit prior to February who will exit the trial at that time.

6 ORGANIZATION OF SAP REVISION

In the interest of providing clarity in updated definitions and methods, the analysis plan has been revised in a manner that acknowledges the early termination decision and the resulting participant follow-up described in Section 5.

7 TRIAL DESIGN CONSIDERATIONS

7.1 Original Trial Design

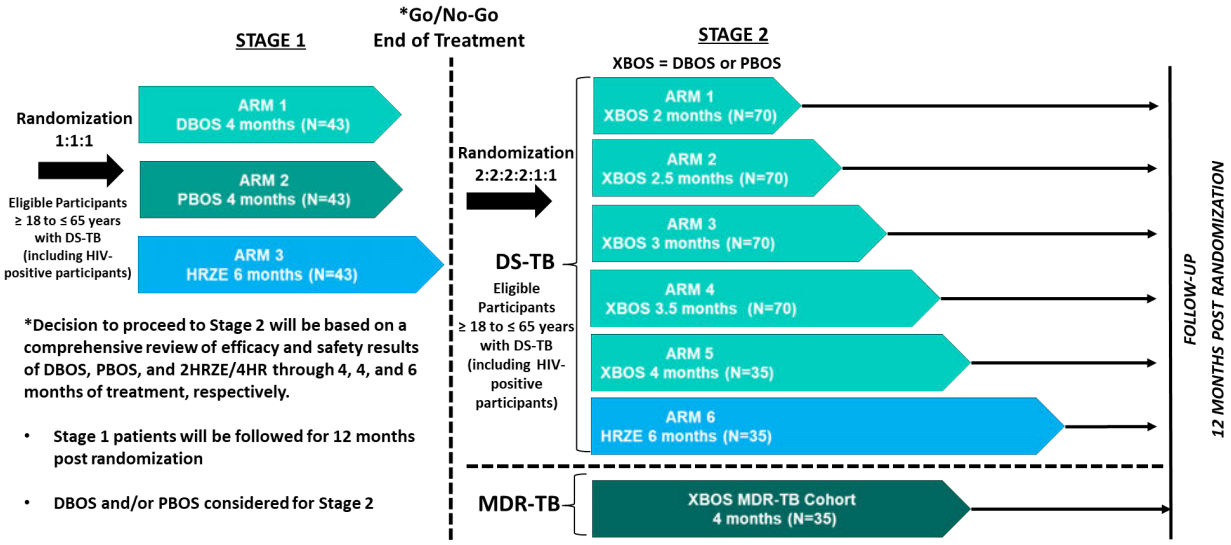
The trial planned for a two-stage Phase 2b/2c design as described below; see protocol for additional details.

In Stage 1/Phase 2b, the safety, tolerability, efficacy, and pharmacokinetics (PK) of DBOS and PBOS administered daily for 4 months (17 weeks) was evaluated in participants ≥ 18 to ≤ 65 years old with pulmonary DS-TB. Approximately 129 participants were to be randomized to receive DBOS, PBOS, or the global DS-TB treatment SOC consisting of 8 weeks of HRZE followed by 18 weeks of HR (hereafter referred to as '2HRZE/4HR' or 'HRZE regimen'). All participants were to be followed through 12 months post-randomization. A structured and systematic capture of important clinical, safety, microbiologic, and radiologic factors to support an Investigator's assessment and decision to stop treatment at the end of a participant's assigned duration of treatment and watch for post-treatment relapse was implemented (termed the "stop treatment and watch" [STrAW] framework). At the end of Stage 1, if either DBOS or PBOS had shown evidence of treatment shortening potential with an acceptable safety profile, then one of the regimens would have been considered for further evaluation in Stage 2; this regimen is labelled as 'XBOS' in the Stage 2 design. Treatment shortening potential was to be evaluated based on the primary and secondary efficacy objectives described in Section 13. Based on an interim evaluation of key efficacy measures, the trial was terminated early.

In Stage 2/Phase 2c, the safety, tolerability, efficacy, and PK of XBOS administered daily across up to 5 treatment durations in the range of 2 to 4 months would have been evaluated relative to 2HRZE/4HR in participants aged ≥ 18 to ≤ 65 years with pulmonary DS-TB. All participants would have been followed through 12 months post-randomization. The STrAW framework also would have been implemented in Stage 2. Stage 2 is no longer planned as a result of early trial termination.

The trial was conducted at multiple sites in multiple countries. Stage 1 was to be conducted in approximately 10 to 13 sites, in approximately 3 countries with diverse geographic representation (likely in Africa, Asia, and South America). The study schema is shown in Figure 1.

Figure 1. Trial Schema



7.2 Trial Population

For Stage 1, participants between 18 and 65 (inclusive) years of age of both sexes were eligible for the trial if they were recently diagnosed (within 8 weeks prior to informed consent), with untreated (≤ 4 days of treatment), microbiologically confirmed, drug susceptible pulmonary TB, as defined by all of the following:

- Confirmation of Mtb infection: Mtb positivity on a molecular test (eg, Xpert Ultra, Hain Line Probe Assay [LPA]) conducted on a sputum specimen for trial screening;
- Evidence of non-paucibacillary disease: ≥ 1+ sputum smear positivity for acid-fast bacilli using fluorescent microscopy, as defined by the International Union Against Tuberculosis and Lung Disease (IUATLD)/WHO scale, OR a Xpert Ultra semi-quantitative result of 'medium' or 'high' on the sputum specimen for trial screening;
- Drug-susceptible TB: Isoniazid and rifampicin resistance not detected, as determined by a molecular test (eg, Hain LPA, Xpert Ultra, Xpert MTB/XDR) conducted on a sputum specimen for trial screening;
- Clinical signs and/or symptoms consistent with active TB in the opinion of the Investigator; and
- Chest radiograph consistent with active TB in the opinion of the Investigator. Note, the Investigator is permitted, but not required, to incorporate a radiologist's interpretation into their assessment of a participant's chest radiograph.

See Section 6.1 and Section 6.2 in the trial protocol for details on all inclusion and exclusion criteria.

A subgroup of participants infected with human immunodeficiency virus (HIV) were enrolled if they were already on permitted antiretroviral treatment (ART) for at least 3 months prior to screening (see Protocol Section 7.5.1.1), their CD4 T-cell count was ≥ 200 cells/μL, their HIV viral load was < 200 copies/mL, and there were no HIV-associated malignancy or clinically significant opportunistic infection (besides TB) present requiring treatment with a prohibited concomitant medication. HIV-infected participants enrolling at a trial site in Peru were not eligible due to the requirement for longer TB treatment courses than the standard 6-month HRZE regimen for patients with HIV/TB co-infection as per the Peruvian national TB treatment guidelines.

7.3 Trial Treatments: Stage 1

The 2 treatment regimens for this Phase 2 clinical trial are: delamanid, bedaquiline, OPC-167832, and sutezolid (DBOS, Regimen 1), and pretomanid, bedaquiline, OPC-167832, and sutezolid (PBOS, Regimen 2). These will be compared to SOC regimen 2HRZE/4HR.

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

- Arm 1 (N = 43 planned): delamanid + bedaquiline + OPC-167832 + sutezolid (DBOS) for 4 months (17 weeks)
- Arm 2 (N = 43 planned): pretomanid + bedaquiline + OPC-167832 + sutezolid (PBOS) for 4 months (17 weeks)
- Arm 3 (N = 43 planned): 2HRZE/4HR for 6 months (26 weeks) (8 weeks of HRZE then 18 weeks of HR)

The actual sample size due to early termination will be summarized in the clinical study report. The dosing schedule and requirements for the investigational regimens (Regimen 1 & Regimen 2) are presented in Table 1 below.

Table 1. Dosing Schedule for Investigational Regimens

Regimen 1* (Stage 1, Arm 1)	D Delamanid	B Bedaquiline	O OPC-167832	S Sutezolid
Dose and Schedule	300 mg once daily (QD) for treatment duration	400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment weeks	30 mg QD for treatment duration	1200 mg QD for treatment duration
Number of pills	6 pills per day	4 pills per day for 2 weeks, then 2 pills thrice weekly	1 pill per day	2 pills per day
Regimen 2* (Stage 1, Arm 2)	P Pretomanid	B Bedaquiline	O OPC-167832	S Sutezolid
Dose and Schedule	200 mg QD for treatment duration	400 mg QD for 2 weeks, then 200 mg thrice weekly for remaining treatment weeks	30 mg QD for treatment duration	1,200 mg QD for treatment duration
Number of pills	1 pill per day	4 pills per day for 2 weeks, then 2 pills thrice weekly	1 pill per day	2 pills per day

* Dosing occurs 7 days per week unless specified otherwise.

The daily dose of HRZE and HR, formulated in a fixed dose combination (FDC), will be based on the participant's weight at screening and during treatment as outlined in Table 2 below. If treatment is interrupted, individual drug(s) in the SOC regimen may be reintroduced. Because drugs in the SOC regimen prescribed individually will be procured locally, the dose units may vary from those in the FDC. This information will be captured on the exposure eCRFs, and the number of pills will be derived from the weight-based dose prescribed and the dose unit.

Table 2. Dosing Schedule for SOC Regimen

Intensive Phase						
Weight Band	Weight Range (kg)[Δ]	Number of FDC Tablets Taken Daily*	Number of Milligrams of Component Drugs Administered			
			Isoniazid	Rifampicin	Pyrazinamide	Ethambutol
1	30-37	2	150	300	800	550
2	38-54	3	225	450	1,200	825
3	55-70	4	300	600	1,600	1,100
4	≥ 71	5	375	750	2,000	1,375
Continuation Phase						
Weight Band	Weight Range (kg)	Number of FDC Tablets Taken Daily*	Number of Milligrams of Component Drugs Administered			
			Isoniazid	Rifampicin		
1	30-37	2	150	300		
2	38-54	3	225	450		
3	55-70	4	300	600		
4	≥ 71	5	375	750		

[Δ] Participant's weight should be rounded down when determining weight band (eg, round 54.9 kg to 54 kg [Weight Band 2]).
* Fixed dose combination (FDC) of 75 mg of isoniazid, 150 mg of rifampicin, 400 mg of pyrazinamide, and 275 mg of ethambutol (HRZE) for the Intensive Phase and 75 mg of isoniazid and 150 mg of rifampicin (HR) for the Continuation Phase will be utilized. Individual agents comprising the HRZE regimen will be utilized for clinical management needs of SOC interruptions, including reintroduction of individual agents with weight-based dosing.
* Dosing occurs 7 days per week unless specified otherwise. WHO treatment guidelines from 2010 and national TB treatment guidelines in countries where trial sites are located serve as the basis for the standard of care dosing schedule.

For analysis and reporting, treatment arms will be presented in tables, listings, and figures with the following labels:

Treatment Arm	Display Label
Delamanid + Bedaquiline + OPC-167832 + Sutezolid for 4 months (17 weeks).	DBOS
Pretomanid + Bedaquiline + OPC-167832 + Sutezolid for 4 months (17 weeks).	PBOS
2HRZE/4HR for 6 months (26 weeks) (8 weeks of HRZE then 18 weeks of HR)	HRZE

7.4 Stop Treatment and Watch (STrAW) Concilium

The STrAW Concilium was established for the trial to provide expert clinical consultation to Investigators for the following purposes:

- For all participants where the Investigator wants to permanently stop one or more trial medications, continue trial treatment past the assigned duration, or restart TB treatment after the completion of trial treatment and
- Other challenging clinical scenarios per the Investigator's judgment.

The STrAW Concilium was composed of independent experts in TB clinical management and experience in the conduct of TB clinical trials. The Concilium operated according to a charter detailing its structure, participants, and procedures. Concilium members were partially blinded to trial regimen assignment. It was not feasible to fully blind Concilium members from whether a participant was assigned an investigational regimen or standard of care due to their different durations of treatment and intensive and continuation phases for 2HRZE/4HR.

7.5 Sample Size Justification: Stage 1

In Stage 1, approximately 43 participants per arm (129 total) were to be randomized in a 1:1:1 ratio to the treatment arms described in Section 7.3. The actual sample size due to early termination will be summarized in the clinical study report.

A subgroup of HIV-infected participants could be enrolled; it was expected that most of these participants would be in South Africa because HIV co-infection is highly prevalent in South Africa but not in other countries planned for trial participation. No cap or minimum number of HIV-infected participants was planned. HIV-infected participants enrolling at a trial site in Peru were not eligible due to the requirement for longer TB treatment courses than the standard 6-month HRZE regimen for patients with HIV/TB co-infection as per the Peruvian national TB treatment guidelines.

The operating characteristics of the Stage 1 primary endpoint (unfavorable outcome rate at end of treatment, defined in Section 13.1) were examined via simulation under binomial distributions with n = 43 per treatment group and true unfavorable outcome probabilities as shown in the first and second columns of Table 3. The third column shows, under assumed exponential distributions, the calculated week at which the XBOS unfavorable outcome probability is equal to that of 2HRZE/4HR. For example, in the row of Table 3 that shows the true unfavorable outcome probability is 0.1 for 2HRZE/4HR at 26 weeks and 0.05 at 17 weeks for XBOS, then XBOS has an unfavorable outcome probability of 0.1 at 13.1 weeks, calculated as follows: $\exp(-\lambda*13.1) = 0.1$ under $\lambda = 0.176$, where the value of λ satisfies the condition $\exp(-\lambda*17) = 0.05$.

Based on simulated data, the final column of Table 3 shows the estimated probability of observing an XBOS unfavorable outcome rate at 17 weeks that is no greater than that of 2HRZE/4HR at 26 weeks. Specifically, with 43 participants per arm, the estimated probability of observing same or improved unfavorable outcome rate with 17 weeks of XBOS relative to 26 weeks of 2HRZE/4HR is 56% to 58% when the underlying probabilities are equal;

75% to 87% when the unfavorable outcome probability for XBOS is 5 percentage points lower than 2HRZE/4HR; and above 89% when the unfavorable outcome probability for XBOS is 10% points lower than 2HRZE/4HR.

It was expected that < 10% of participants could have pre-treatment baseline sputum culture results negative for growth of drug-susceptible (defined as susceptible to both isoniazid and rifampicin) Mtb. Such participants were not replaced with extended enrollment. Accounting for exclusion of these participants from the randomized population, the operating characteristics with n = 40 per treatment group are similar to those summarized above.

Table 3. Operating Characteristics of Unfavorable Outcome at End of Treatment

Unfavorable Outcome Probability With n = 43 per Treatment Group			
True 2HRZE/4HR at 26 Weeks	**True XBOS at 17 Weeks**	**Calculated Week When XBOS = 26-Week 2HRZE/4HR[a]**	**Estimated Probability That XBOS at 17 Weeks ≤ 2HRZE/4HR at 26 Weeks[b]**
0.10	0.10	17.0	0.58
	0.05	13.1	0.87
0.15	0.15	17.0	0.57
	0.10	14.0	0.81
	0.05	10.8	0.97
0.20	0.20	17.0	0.56
	0.15	14.8	0.75
	0.10	12.7	0.89

a. Based on exponential distribution for the probability of unfavorable outcome over time on treatment.
b. Proportion of 5,000 binomial paired simulations for which the number of XBOS participants with unfavorable outcome is ≤ the number of 2HRZE/4HR participants with unfavorable outcome (PASS 2022).

7.6 Stratification Factors

The trial was stratified by the following two factors:

- Country/HIV status with four levels: (1) Peru, (2) Philippines, (3) South Africa and HIV positive, and (4) South Africa and HIV negative; and
- TB disease severity measured by extent of disease on screening chest X-ray (CXR) and mycobacterial burden on screening sputum smear and Xpert Ultra, categorized as follows with two levels:
    1. High severity: > 2 lung zones involved on screening CXR or screening sputum smear of 3+ or screening sputum Xpert Ultra cycle threshold > 0 and < 18.

2. Low/medium severity: ≤ 2 lung zones involved on screening CXR and screening sputum smear of ≤ 2+ and screening sputum Xpert Ultra cycle threshold ≥ 18.

The lowest of 5 Xpert Ultra cycle threshold values was to be used for the TB disease severity stratification factor. As noted, it was expected that most of the HIV-infected participants would be in South Africa because HIV co-infection is highly prevalent in South Africa but not in other countries planned for trial participation. No enrollment occurred in Peru due to early trial termination.

7.7 Randomization: Stage 1

This trial utilized a stratified randomization scheme. Participants were randomized in a 1:1:1 ratio to either DBOS for 4 months (17 weeks), PBOS for 4 months (17 weeks), or 2HRZE/4HR for 6 months (26 weeks), using a permuted block design static randomization schedule with variable block size and capping by treatment arm to minimize overall imbalance. Participants were stratified by Country/HIV Status and TB Disease Severity, as defined in Section 7.6. Participants randomized in South Africa had their HIV status taken into account during stratification to ensure balance within the HIV subgroups in South Africa, whereas participants in Peru or Philippines were to be balanced within country without regard to HIV status. No enrollment cap was be applied to the HIV-infected subgroup. No enrollment occurred in Peru due to early trial termination. Refer to randomization plan for further details.

7.8 Masking (Blinding)

This trial is open-label for trial participants, trial site personnel, IDMC members, and Sponsor and CRO personnel. Microbiology lab personnel are blinded to all trial participants' regimen assignments. Members of the STrAW Concilium (Section 7.4) will be blinded to the regimen assignment in their review of the data reports. However, because of the different treatment durations for the investigational regimens vs. SOC, it is not feasible to fully blind laboratory staff or Concilium members to a given participant's treatment assignment after their post-randomization follow-up has exceeded 4 months.

8 TRIAL OBJECTIVES AND ENDPOINTS (STAGE 1)

This section describes the trial objectives that are addressed in this SAP. The table includes a high-level description of updates for the early trial termination shown, if applicable. Details of these update are included of the main body.

8.1 Primary Objectives

Objectives	Endpoint	Updates Based on Early Trial Termination
Safety		
• To characterize the safety and tolerability of the combination regimens of DBOS and PBOS administered for 4 months compared to 2HRZE/4HR through the end of treatment in participants with pulmonary DS-TB	• Proportion of participants with Severe AEs (≥ Grade 3) and SAEs through 2 weeks after the end of treatment	• None
Efficacy		
• To assess treatment shortening potential of the combination regimen of DBOS relative to 2HRZE/4HR in participants with pulmonary DS-TB	• Proportion of participants with unfavorable outcome status through end of treatment for each arm	• Modified per protocol population added • Modified Intention-to-Treat population removed • Primary analysis unadjusted for stratification factors
• To assess treatment shortening potential of the combination regimen of PBOS relative to 2HRZE/4HR in participants with pulmonary DS-TB	• Proportion of participants with unfavorable outcome status through end of treatment for each arm	• Modified per protocol population added • Modified Intention-to-Treat population removed

8.2 Secondary Objectives

As indicated in the table below, the analyses to support the PK objectives will be addressed in a separate PK SAP.

Objectives	Endpoint	SAP or PK SAP	Updates Based on Early Trial Termination
Safety			
• To assess the safety and tolerability of the combination regimens of DBOS and PBOS administered for 4 months compared to 2HRZE/4HR over 12 months	• Proportion of participants in each arm with: o All-cause permanent trial treatment discontinuation o Severe AEs (≥ Grade 3) and SAEs through the end of the post treatment follow up period (12 months post randomization)	SAP	None
• To assess safety and tolerability of the combination regimens of DBOS and PBOS relative to 2HRZE/4HR in participants with pulmonary DS-TB and HIV co-infection	• In the subset of HIV-infected participants, proportion of participants in each arm with: o Severe AEs (≥ Grade 3) and SAEs through 2 weeks after the end of treatment o Severe AEs (≥ Grade 3) and SAEs through the end of the post treatment follow up period (12 months post randomization) o All-cause treatment discontinuation	SAP	Removed due to small sample size of HIV-infected participants
Efficacy			
• To assess the efficacy of the combination regimens of DBOS and PBOS relative to 2HRZE/4HR in participants with pulmonary DS-TB at the end of post treatment follow-up period (12 months post-randomization)	• Proportion of participants with unfavorable outcome status in each treatment arm at the end of post treatment follow-up period (12 months post-randomization)	SAP	• Modified per protocol population added • Modified Intention-to-Treat population removed
• To assess the efficacy of the combination regimens of DBOS and PBOS relative to 2HRZE/4HR in participants with DS-TB and HIV co-infection at the end of treatment and the end of the post treatment follow up period (12 months post-randomization)	• In participants with HIV co-infection: o Proportion of participants with unfavorable outcome status in each treatment arm at the end of treatment o Proportion of participants with unfavorable outcome status in each treatment arm at the end of post treatment follow-up period (12 months post-randomization)	SAP	Removed due to small sample size of HIV-infected participants
• To investigate the efficacy of the DBOS and	• Proportion of participants with unfavorable outcome status in all arms	SAP	Removed

Objectives	Endpoint	SAP or PK SAP	Updates Based on Early Trial Termination
PBOS relative to 2HRZE/4HR at 6 months after randomized treatment duration	at 6 months after randomized treatment duration (10 months post-randomization for DBOS/PBOS and 12 months post-randomization for 2HRZE/4HR)		
• To evaluate and compare the change in Mycobacteria Growth Indicator Tube® (MGIT) culture outcomes in participants receiving the combination regimens of DBOS and PBOS relative to 2HRZE/4HR	• Time to sustained sputum culture conversion to negative for Mtb growth in MGIT • Sputum culture time to detection (TTD) curves in MGIT through 4, 8, 9, 13, and 17 weeks of treatment • Sputum culture status for Mtb growth in MGIT at all time points at which sputum culture is assessed during the treatment period	SAP PK SAP will address modelling with PK parameters such as AUC	• Modified per protocol population added • Modified Intention-to-Treat population removed • Week 8 removed
• To evaluate and compare the change in solid culture outcomes in participants receiving the combination regimens of DBOS and PBOS relative to 2HRZE/4HR	• Time to sustained sputum culture conversion to negative in solid culture during treatment period • Sustained sputum culture conversion to negative for Mtb growth in solid culture at all time points at which sputum culture is assessed during treatment period	SAP	• Modified per protocol population added • Modified Intention-to-Treat population removed
• To evaluate emergence of antiTB drug resistance.	• Resistance result among baseline sputum culture and first culture positive for Mtb at Week 13 or afterwards through 12 months post randomization for delamanid, bedaquiline, isoniazid, rifampicin, pyrazinamide, and/or ethambutol through 12 months post randomization. • MIC values of delamanid, pretomanid, bedaquiline, OPC-167832, and sutezolid performed on baseline sputum culture and first culture positive for Mtb at Week 13 or afterwards through 12 months post randomization.	SAP	None
Pharmacokinetics			
• To evaluate the pharmacokinetics of the individual components of the DBOS and PBOS regimens in all participants with pulmonary DS-TB. • To assess the drug-drug interactions (DDI) of	• Concentrations of individual anti-TB agents comprising the combination regimens including: o Delamanid and its metabolite DM-6705, bedaquiline and its metabolite M2, OPC-167832, and sutezolid and its active metabolite PNU-101603 for DBOS.	PK SAP	None

Objectives	Endpoint	SAP or PK SAP	Updates Based on Early Trial Termination
antiretroviral medications with the experimental TB regimens in participants with DS-TB and HIV co-infection.	○ Pretomanid, bedaquiline and its metabolite M2, OPC—167832, and sutezolid and its active metabolite PNU-101603 for PBOS. • For HIV co-infected participants: ○ Concentrations of individual antiretroviral medications.		

8.3 Exploratory Objectives

As indicated in the table below, some exploratory objectives described in the protocol will be summarized in the clinical study report and are therefore addressed in this SAP, while others will be addressed in a separate exploratory SAP (ESAP). Revisions to the exploratory analyses, if any, will be addressed in the ESAP.

Objectives	Endpoint	SAP or ESAP	Updates Based on Early Trial Termination
[redacted]	[redacted]	ESAP	TBD
		SAP/ESAP	None for SAP analyses
		ESAP	TBD
		ESAP	TBD

Objectives	Endpoint	SAP or ESAP	Updates Based on Early Trial Termination
[redacted]	[redacted]	ESAP	TBD
[redacted]	[redacted]	SAP	
[redacted]	[redacted]	ESAP	

9 TRIAL ANALYSIS POPULATIONS

A summary table containing the number of participants in each of the populations defined below along with any reasons for exclusions will be provided. The Modified Intention-To-Treat (mITT) analysis population is no longer planned. Section 12.1 provides additional details regarding participant disposition.

Analysis Population	Description
Randomized Population	All participants randomly assigned to trial intervention. A participant will be programmatically included in the Randomized analysis population if the participant has a randomization number and date. Participants will be analyzed according to the intervention to which they were randomized.
Safety Population	All participants randomly assigned to trial intervention, who received at least one dose of the trial intervention. This includes any component of the treatment regimen. Participants will be analyzed according to the intervention they actually received.
Per Protocol (PP) Population	All participants randomly assigned to trial intervention, who received the trial intervention, have DS-TB that is confirmed as sputum culture positive at baseline (from either MGIT liquid culture or solid media culture), and did not substantially deviate from the protocol procedures. Treatment discontinuation resulting from early trial termination will be considered per protocol. Participants will be analyzed according to the intervention they actually received.
Modified PP Population	All participants in the PP population excluding those discontinued DBOS, PBOS, or HRZE due to early trial termination.
PK Population	Participants with at least one quantified plasma PK sample.
Women of Childbearing Potential (WOCBP)	Includes a subset of randomized premenopausal female participants who are capable of becoming pregnant following menarche.

Within the Safety, PP, Modified PP, and PK populations, a participant will be classified in the randomized treatment group unless they received an incorrect treatment regimen for the entire treatment period or up to last dose received, in which case the participant's treatment group will be defined as the incorrect regimen they actually received.

10 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

The early trial termination and resulting change in treatment and follow-up as described in Section 5 will have an impact on some of the original analyses described in the protocol and in the previous version of the SAP. Details of the necessary adjustments to the analyses are provided in the relevant sections of this version of the SAP.

11 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

11.1 Data Display Conventions

Change from baseline (CFB) will be calculated as the difference, T minus B, where T is the value on treatment and B is the baseline value. CFB will be computed for participants who have both a baseline value and a post-baseline value. Missing data conventions are described in Section 11.6. For parameters that are not fully numeric, CFB will not be computed, and values will be summarized in a listing and shift tables where applicable.

The day when a participant receives the first dose of trial intervention is defined as Trial Day 1 or Day 1. All other trial days will be computed relative to Day 1. For an event that occurs on or after Day 1, trial day for the date associated with the event will be calculated as $Date_{event} - Date_{Day\ 1} + 1$. For events before Day 1, trial day for a particular event will be calculated as $Date_{event} - Date_{Day\ 1}$. Day 0 will not be used.

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated using descriptive statistics. For categorical variables, summary tables will be provided giving sample size and relative frequency. For continuous variables, summary tables will be provided giving sample size, arithmetic mean, geometric mean (if appropriate), standard deviation, coefficient of variation (if appropriate), median, minimum, and maximum.

The following conventions for decimal precision will be applied when presented in listings or plotted in figures. However, the reported results may be rounded if appropriate to obtain an organized and understandable display. Results shown in tables will be rounded to one decimal place, as applicable.

- Mean will contain one more decimal place than actual values.
- Median will contain one more decimal place than actual values.
- SD will contain two more decimal places than the actual values.
- Percentiles, minimum, and maximum will have the same precision as the actual values.
- For the derived values, the decimal precision will be limited to 2 decimal places for mean/median and 3 decimal places for SD.
- Percentages will be displayed with one decimal place and percentages for zero counts will be omitted from the presented results. If the percentage is greater than 0 but rounds to 0.0% (eg, 0.04%), display as "(< 0.1)".

Statistical analyses of safety and efficacy data will be performed using SAS software Version 9.4 or higher, except for statistical modelling which may be performed using R.

11.2 Adjustments for Multiple Comparisons and Control of Type 1 Error

All Stage 1 analyses will be descriptive; no formal hypothesis testing will be performed. Tabular presentations of efficacy analyses will include point estimates along with 95% confidence intervals (CI) for each treatment group, and for select endpoints the estimated difference will

also be calculated to characterize the treatment effect of DBOS vs. 2HRZE/4HR and PBOS vs. 2HRZE/4HR. Safety presentations will include frequencies and percentages.

No adjustments will be made for the descriptive comparisons of multiple outcome measures.

11.3 Baseline Definition

Baseline is defined as the last assessment made prior to the first administered dose of trial medication. In some presentations, both the screening result as well as baseline will be summarized. For sputum culture positivity and drug susceptibility testing, baseline also includes up to Week 1 assessments. In special cases where a Day 1 assessment is planned to be conducted prior to the first dose of trial medication, but the time of the assessment is not recorded on the eCRF, the Day 1 assessment will be assumed to be the baseline assessment.

11.4 Visit Windows/Unscheduled Visits

In analyses of data summarized by trial visit, dates associated with endpoints being analyzed will be categorized into visit windows, as shown in Table 4. Unscheduled, early termination, and follow-up visits will also be assigned a trial visit where data are scheduled for collection based on the actual days relative to baseline. Unless otherwise specified, if multiple visits fall in the analysis visit window the one closest to the target day will be used. If 2 visits are equidistant to the target day, then the later visit will be used. Handling of safety and efficacy endpoints within visit windows will follow the approaches detailed below.

Safety parameters:

- Within each visit window, if multiple test records are available, the one with the worst toxicity grade will be selected.
- If multiple records have the same toxicity grade, the record closest to the target day will be used.
- For lab tests that have both high and low toxicity grades, the record closest to the target day will be selected.

ECG parameters:

- Within each visit window, if multiple test records are available, the one with the highest QTcF value will be selected.
- If multiple records have the same QTcF value, the record closest to the target day will be used.
- ECG parameters presented in summaries will be anchored to the QTcF value timepoint as described above.

Efficacy parameters:

If multiple records fall within the visit window, selection will be based on a ranking system (using Table 7 for derivation of the culture results) rather than proximity to the target date:

1. Mtb-positive results (if available) will be used.
2. If no Mtb-positive results are present, the most recent Mtb-negative result will be selected.
3. If neither Mtb-positive nor Mtb-negative results exist, but at least one contaminated result is available, that will be chosen.
4. If no positive, negative, or contaminated results are present, the remaining unevaluable records will be used.

In addition, a second set of visit labels will be created for which the following conventions will be applied in listings and participant-specific displays. For participants who have early discontinuation from treatment, including those whose treatment is discontinued as a result of early trial termination, the visit associated with end of treatment will be labelled as "Week X/EOT" or "Week X/EOT TT" if treatment discontinuation was due to early trial termination, where Week X is the next scheduled visit. For participants who withdraw early from the trial, the visit associated with early termination from the trial will be labelled as "Week X/ET" or "Week X/ET TT", if participant's early termination was due to early termination of the trial, where Week X is the next scheduled visit.

Table 4. Analysis Visit Windows for Assessments

Protocol Visit Label	Analysis Visit Label	Target Study Day	Visit Window
Visit 1/2	Screening/Baseline	Last assessment date before first dose – first dose date	≤ Day 1
Visit 3 dosing	First dose date	1	—
Visit 3 assessments	Week 1	8	Day 1-12
Visit 4	Week 2	15	Day 13-22
Visit 5	Week 4	29	Day 23-36
Visit 6	Week 6	43	Day 37-50
Visit 7	Week 8	57	Day 51-60
Visit 8	Week 9	64	Day 61-71
Visit 9	Week 11	78	Day 72-85
Visit 10	Week 13	92	Day 86-99
Visit 11	Week 15	106	Day 100-113
Visit 12	Week 17	120	Day 114-127
Visit 13	Week 19	134	Day 128-141
Visit 14	Week 21	148	Day 142-155
Visit 15	Week 23	162	Day 156-172
Visit 16	Week 26	183	Day 173-190
Visit 17	Week 28	197	Day 191-204

Protocol Visit Label	Analysis Visit Label	Target Study Day	Visit Window
Visit 18	Month 7	211	Day 205-226
Visit 19	Month 8	241	Day 227-256
Visit 20	Month 9	271	Day 257-286
Visit 21	Month 10	301	Day 287-316
Visit 22	Month 11	331	Day 317-346
Visit 23	Month 12	361	Day 347-376

11.5 Microbiology Data for Efficacy Endpoints

11.5.1 Sputum Culture Data

Up to 2 sputum specimens will be collected at each visit of the trial for purposes of primary and secondary endpoint analyses. Each specimen will be inoculated on liquid, undiluted solid, and diluted solid culture media, for a potential of up to 6 individual culture results per time point. Note that on 21 June 2024, laboratories were advised to discontinue diluted LJ cultures for visits occurring after Week 28. The microbiology laboratory will report each culture result, based on liquid Mycobacteria Growth Indicator Tube (MGIT) or solid media, as shown in the first column of Table 5, and will be classified as Positive for Mtb, Negative for Mtb, Contaminated, or Unevaluable.

Table 5. Derivation of Individual Liquid (MGIT) or Solid Culture Result

Individual Lab Culture Result (raw data)	Classification for Analysis (derived)
Positive for MTB Complex (3+, 2+, 1+, < 10 for solid media)	Positive for Mtb
Positive for MTB Complex with contamination	
Positive for MTB and NTM	
Positive for NTM	Negative for Mtb
Negative for MTB Complex	
Contaminated	Contaminated
No Result	Unevaluable
Other (Specify)	

Culture results for a visit window will be derived from any of the cultures (liquid or solid) performed at that visit window, according to Table 6 and Table 7 below.

Table 6. Derivation for Each Culture Type (Final Liquid or Solid Culture Results) for Each Visit Window

Definition Using All Available Individual Culture Results From the Same Visit (derived – see table above)	Classification of Visit Culture Result (derived)
Any of up to the number of expected culture results by culture type (2 MGIT or 4 LJ) are "Positive for Mtb"	Mtb culture positive
At least one culture result is "Negative for Mtb" and all other cultures are non-positive for Mtb	Mtb culture negative
All reported cultures are "Contaminated" or a combination of "Contaminated" and "Unevaluable"	Culture contaminated
All reported cultures are "Unevaluable"	Unevaluable

Table 7. Derivation of Composite Final Liquid and Solid Culture Results for Each Visit Window

Definition Using Up to Six Individual Culture Results From the Same Visit (derived – see Table 5)	Classification of Visit Culture Result (derived)
Any of culture results within a visit window are "Positive for Mtb"	Mtb culture positive
At least one culture result within a visit window is "Negative for Mtb" and all other cultures are non-positive for Mtb	Mtb culture negative
All reported cultures within a visit window are "Contaminated" or a combination of "Contaminated" and "Unevaluable"	Culture contaminated
All reported cultures within a visit window are "Unevaluable"	Unevaluable

11.5.2 Whole Genome Sequencing Data

Whole Genome Sequencing (WGS) was scheduled to be performed per the protocol's Schedule of Assessments (Appendix 1) on an Mtb-positive culture from baseline visit or Week 1, depending on suitability of culture growth. Additionally, WGS was to be conducted on the first of any subsequent Mtb-positive culture obtained from sputum samples collected at any visit from the end of treatment through Month 12 for suspected relapse cases (the post-treatment follow-up period begins at Week 17 for XBOS Arms and at Week 26 for HRZE Arm).

For participants randomized to the HRZE arm, WGS was also performed on Mtb-positive cultures from Week 17 through Week 23 to assess microbiologic failure, contributing to unfavorable outcome status as defined in Section 11.3.1 of the Protocol.

Furthermore, due to the early termination of the trial following emerging efficacy data (see Section 5), additional WGS testing was conducted at the Sponsor's request, including for key on-treatment culture isolates. The WGS data was used to support the derivation of unfavorable outcome status by determining whether Mtb-positive cultures collected at Week 17 or later contain Mtb strains that are indistinguishable from baseline strains.

For each tested culture isolate, WGS data output includes sample identifiers, a comparison of SNP differences between each isolate tested for a given participant, and the lineage(s) of each isolate. For the purpose of determining microbiologic unfavorable outcome status associated

with an Mtb-positive culture at a given post-baseline visit, strain relatedness of that culture will be derived from all pairwise SNP differences between the strains from the post-baseline visit and the baseline strains, where strain relatedness is defined as follows:

- Definition of Strain Relatedness:
  - If SNP difference < 10: Strains are classified as "indistinguishable" or "same strain."
  - If SNP difference ≥ 10: Strains are classified as "different strains."

For example:

- If BSL_1 and Week17_2 SNP difference = 3, these strains are classified as "indistinguishable" or "same strain."
- If BSL_1 and Week21_2 SNP difference = 312, these strains are classified as "different strains."

If no strains from a given post-baseline visit are indistinguishable from any baseline strain from the same participant, that visit is considered a "Positive Culture with different strain from baseline". Refer to Table 8 for derivation of microbiologic unfavorable outcome status based on a single EOT or later WGS result. Refer to Table 9 for derivation of microbiologic unfavourable outcome status based on WGS results from multiple study visits at EOT and later for all arms, and for EOT UOS for HRZE arm (Week 17-Week 26).

11.5.2 Derivation of Microbiologic Unfavorable Outcome Status

Microbiologic UOS will be derived for each post-baseline visit (UOS at Visit X), and the overall UOS will then be derived across visits. These derivations are shown below in Table 8 and Table 9, respectively.

The assumptions underlying the derivations are as follows:

- The composite culture classifications for each sputum sample collected during the visit window and their respective WGS SNP difference results will be used in determining microbiologic unfavorable outcome status (mUOS) at that visit/timepoint even if multiple visits occur during a visit window.
- A SNP difference < 10 will always result in an unfavorable mUOS for that timepoint. If all available SNP differences for a timepoint are ≥ 10 then the timepoint under evaluation for mUOS is not unfavorable. If there is an Mtb-positive composite culture classification at a timepoint but no available SNP difference result for interpretation (ie, missing WGS result), then the timepoint under evaluation for mUOS is unfavorable.
- Genotyping data obtained from a sputum culture taken from Week 15 visit window or earlier will not be used in the determination of mUOS.
- Composite sputum culture classifications from the Week 15 visit window or earlier (excluding WGS results from these visits) will be used (per Table 10 of the SAP) if all Week 17 sputum results are unevaluable or contaminated.

- If BSL composite culture interpretation is negative or uninterpretable, and Week 1 composite culture interpretation is Mtb Positive, comparison of SNP differences will be between WGS results from the EOT visit and the Week 1 visit.

Table 8. Deriving Timepoint Microbiologic Unfavorable Outcome Status (eg, At XBOS EOT [Week 17] for Primary Efficacy Analysis and HRZE EOT [Week 26] for Sensitivity Analysis)

Scenario	Sputum #	Composite Culture Classification*	WGS SNP difference	SNP Interpretation (derived)	Sputum # Micro UO Status (derived)	Timepoint Micro UO Status (derived)	Rationale
1	A	Positive	SNP ≥ 10	Not indistinguishable	Not unfavorable	Not unfavorable	SNP interpretation(s) is/are available, and all is/are ≥ 10
	B	Positive	Missing	N/A – Missing	Unfavorable		
2	A	Negative	N/A (Neg)	N/A - Negative	Not unfavorable	Unfavorable	No SNP interpretation available when expected
	B	Positive	Missing	N/A – Missing	Unfavorable		
3	A	Positive	SNP < 10	Indistinguishable	Unfavorable	Unfavorable	SNP < 10
	B	Positive	SNP ≥ 10	Not indistinguishable	Not unfavorable		
4	A	Positive	SNP ≥ 10	Not indistinguishable	Not unfavorable	Not unfavorable	SNP interpretation(s) is/are available, and all is/are ≥ 10
	B	Positive	SNP ≥ 10	Not indistinguishable	Not unfavorable		
5	A	Positive	SNP < 10	Indistinguishable	Unfavorable	Unfavorable	SNP < 10
	B	Positive	SNP < 10	Indistinguishable	Unfavorable		
6	A	Positive	Missing	N/A – Missing	Unfavorable	Unfavorable	No SNP interpretation available when expected
	B	Positive	Missing	N/A – Missing	Unfavorable		
7	A	Positive	SNP < 10	Indistinguishable	Unfavorable	Unfavorable	SNP < 10
	B	Positive	Missing	N/A – Missing	Unfavorable		

Scenario	Sputum #	Composite Culture Classification*	WGS SNP difference	SNP Interpretation (derived)	Sputum # Micro UO Status (derived)	Timepoint Micro UO Status (derived)	Rationale
8	A	Negative	N/A (Neg)	N/A – Negative	Not unfavorable	Unfavorable	SNP < 10
	B	Positive	SNP < 10	Indistinguishable	Unfavorable		
9	A	Negative	N/A (Neg)	N/A - Negative	Not unfavorable	Not unfavorable	No positive culture classification
	B	Negative	N/A (Neg)	N/A - Negative	Not unfavorable		
10	A	Positive	SNP ≥ 10	Not indistinguishable	Not unfavorable	Not unfavorable	SNP interpretation(s) is/are available, and all is/are ≥ 10
	B	Negative	N/A (Neg)	N/A - Negative	Not unfavorable		
11	A	Positive	Missing	N/A – Missing	Unfavorable	Unfavorable	No SNP interpretation available when expected
	B	Negative	N/A (Neg)	N/A - Negative	Not unfavorable		
12	A	Positive	SNP < 10	Indistinguishable	Unfavorable	Unfavorable	SNP < 10
	B	Contaminated	N/A (Cont)	N/A – Contaminated	Contaminated		
13	A	Positive	SNP ≥ 10	Not indistinguishable	Not unfavorable	Not unfavorable	SNP interpretation(s) is/are available, and all is/are ≥ 10
	B	Contaminated	N/A (Cont)	N/A – Contaminated	Contaminated		
14	A	Positive	Missing	N/A – Missing	Unfavorable	Unfavorable	No SNP interpretation available when expected
	B	Contaminated	N/A (Cont)	N/A – Contaminated	Contaminated		
15	A	Negative	N/A (Neg)	N/A - Negative	Not unfavorable	Not unfavorable	No positive culture classification
	B	Contaminated	N/A (Cont)	N/A – Contaminated	Contaminated		

Scenario	Sputum #	Composite Culture Classification*	WGS SNP difference	SNP Interpretation (derived)	Sputum # Micro UO Status (derived)	Timepoint Micro UO Status (derived)	Rationale
16**	A	Contaminated	N/A (Cont)	N/A – Contaminated	Contaminated	Contaminated**	No evaluable culture
	B	Contaminated	N/A (Cont)	N/A – Contaminated	Contaminated		
17	A	Positive	SNP < 10	Indistinguishable	Unfavorable	Unfavorable	SNP < 10
	B	Unevaluable	N/A (Uneval)	N/A – Uneval	Unevaluable		
18	A	Positive	SNP ≥ 10	Not indistinguishable	Not unfavorable	Not unfavorable	SNP interpretation(s) is/are available, and all is/are ≥ 10
	B	Unevaluable	N/A (Miss)	N/A – Missing	Unevaluable		
19	A	Positive	Missing	N/A – Missing	Unfavorable	Unfavorable	No SNP interpretation available when expected
	B	Unevaluable	N/A (Miss)	N/A – Missing	Unevaluable		
20	A	Negative	N/A (Neg)	N/A - Negative	Not unfavorable	Not unfavorable	No positive culture classification
	B	Unevaluable	N/A (Uneval)	N/A – Missing	Unevaluable		
21**	A	Unevaluable	N/A (Uneval)	N/A – Missing	Unevaluable	Unevaluable**	No evaluable culture
	B	Unevaluable	N/A (Miss)	N/A – Missing	Unevaluable		

Cont = Contaminated; Miss = Missing; Neg = Negative; SNP = Single nucleotide polymorphism; Uneval = Unevaluable; UO = Unfavorable outcome.
* See Table 7: Derivation of Composite Final Liquid and Solid Culture Results for Each Visit.
**See Table 10: Microbiologic Unfavorable Outcome Status Algorithm at Interim Timepoints Ignoring Whole Genome Sequencing

Table 9. Deriving Microbiologic Unfavorable Outcome Status Across Timepoints (eg, For HRZE Arm Weeks 17-26 for Primary Efficacy Analysis and For All Arms Week 17 – Month 12 for Secondary Efficacy Analysis)

Scenario	Timepoint	Timepoint Micro UO	Micro UO Status Across Timepoints
1	A	Not unfavorable	Unfavorable
	B	Unfavorable	
2	A	Unfavorable	Unfavorable
	B	Unfavorable	
3	A	Not unfavorable	Not unfavorable
	B	Not unfavorable	
4	A	Not unfavorable	Not unfavorable
	B	Unevaluable	
5	A	Unfavorable	Unfavorable
	B	Unevaluable	
6**	A	Unevaluable	Unevaluable**
	B	Unevaluable	

UOS = Unfavorable outcome status.
** See Table 10: Microbiologic Unfavorable Outcome Status Algorithm at Interim Timepoints Ignoring Whole Genome Sequencing.

11.6 Handling of Partial or Missing Data

11.6.1 Incomplete Follow-up or Missing Visits

Participants may not have their scheduled visits as planned for reasons that include skipped visits, loss to follow-up, withdrawal of consent, and early termination. Efficacy analyses will include participants who have non-missing data at the necessary visit(s), subject to the imputation rules described in this section. As applicable, denominators for percentage calculations will be displayed to convey the number of participants included in the analysis.

11.6.2 Missing or Partial Dates for Adverse Events (AEs)

Missing or partial AE start dates will be imputed for the purpose of determining whether the AEs are treatment emergent. Data handling rules for missing or partial start/stop date for AEs are detailed in Appendix 2. The missing or partial dates will be displayed in the data listings as reported on the electronic case report form (eCRF) rather than the imputed dates.

11.6.3 Missing or Partial Dates for Medications

Missing or partial medication start or stop dates will be imputed for the purpose of determining whether the medication is taken concomitantly. Data handling rules for missing or partial start/stop date medications are detailed in Appendix 2. The missing or partial dates will be displayed in the data listings as reported on the eCRF rather than the imputed dates.

11.6.4 Missing or Inconclusive Sputum Results

Missing or inconclusive sputum results will affect the evaluation of microbiologic unfavorable outcome status. A missing result can arise from a missed visit or a missed sputum sample. A missing or inconclusive result may refer to a sputum result that is “Contaminated” or “Unevaluable”, as noted in Table 5. For primary efficacy analysis, visits with contaminated or unevaluable sputum results for the whole visit (as derived per Table 6) will make use of available sputum results from previous visit windows in the derivation of microbiologic unfavorable outcome status. However, WGS data from the Week 15 visit window or earlier will not be used to address missing SNP difference results for Week 17 or later.

Section 11.5.2 provides the derivation of unfavorable outcome status, including handling of missing, contaminated, or unevaluable results.

Table 10 below summarizes the possible scenarios and the algorithm to follow in determining the microbiologic unfavorable outcome status at interim timepoints for participants with missing sputum results. A sensitivity analysis will be performed to assess the impact of this approach. See Section 13.2.4 for details.

Some definitions:

- Refer to Section 13.3.4 for definition of sustained sputum culture conversion (SSCC).
- Visit A: the visit for which the unfavorable outcome status is being assessed.
- Visit A_{-x}: the x^{th} visit prior to Visit A.

- Visit A_{-1} must be at least 5 days and no more than 21 days prior to Visit A.

Table 10. Microbiologic Unfavorable Outcome Status Algorithm at Interim Timepoints Ignoring Whole Genome Sequencing (for Week 15 timepoint, Week 17 timepoint if Unevaluable, Sensitivity Analysis 1, and Supplementary Analysis 2)

Derived Culture Interpretation for Visit A, Regardless of Visit A Genotyping Result	Culture Conversion Status/Derived Culture Interpretation at Study Visit A_{-1}	Final Microbiologic Unfavorable Outcome Status Interpretation at Visit A
Mtb Positive	Not applicable	Unfavorable
Mtb Negative	Not applicable	Not unfavorable
Contaminated or Unevaluable (includes missing visit and missing samples)	A_{-1} is positive	Unfavorable
	A_{-1} is negative	Not unfavorable
	A_{-1} is contaminated/unevaluable and last interpretable culture from A_{-2} or earlier is positive	Unfavorable
	A_{-1} is contaminated/unevaluable and prior sustained SCC up to A_{-2}	Not unfavorable
	A_{-1} is contaminated/unevaluable, and A_{-2} is negative	Not unfavorable
	A_{-1} is contaminated/unevaluable, and A_{-2} is contaminated/unevaluable, and A_{-3} is negative (but not sustained SCC)	Not unfavorable
	A_{-1} is contaminated/unevaluable, and A_{-2} is contaminated/unevaluable and prior sustained SCC up to A_{-3}	Not unfavorable

Sustained SCC = sustained sputum culture conversion.

11.7 Pooling Strategy for Trial Sites

All data will be pooled across trial sites for analysis.

12 TRIAL POPULATION SUMMARIES

12.1 Participant Disposition

Participants' disposition will be listed and summarized for the following trial phases:

Screening Phase:

The numbers and percentages of participants who were screened, rescreened, screen failures, and reasons for screen failure will be summarized. For the participants whose reason for screen failure is "Entry criteria not met", the specific criteria not met will be summarized too. For computing percentages, the denominator will be the number of participants screened**.**

Trial Treatment Phase:

The number and percentages of participants in the following disposition categories will be summarized in a summary table by treatment arm and overall for the randomized population:

- Participants randomized
- Participants randomized and not treated
- Participants who completed treatment
- Participants who had drug interruption
  - Participants who had drug interruption but did not permanently discontinue treatment
- Participants who discontinued treatment
  - Reason for discontinuation of treatment
  - Participants who discontinued treatment but completed trial
- Participants who completed the trial, ie, participants who have their 12-month post-randomization visit
- Participants who withdrew early from the trial
  - Reasons for early withdrawal from the trial

For computing percentages, the denominator will be the number of participants randomized in each treatment arm.

A separate table summarizing the number and percentage of randomized participants in each of the populations; Randomized, Safety, PP, Modified PP, PK, and WOCBP populations will be presented. Additionally, the reasons for exclusion from each population will be displayed. For computing percentages, the denominator will be the number of participants randomized to each treatment arm.

The following listings will also be provided:

- A listing of randomized participants, indicating randomization date, completion status, stratifying factors, and treatment arm assignment.
- A listing of screen failures indicating consent date, inclusion/exclusion, and reason(s) for screen failure.
- Any trial reported deaths indicating death dates, death reason and relationship to trial treatment.
- A listing of participants excluded from the populations and reasons for exclusion.

12.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment arm for participants in the Randomized, Modified PP, and Safety populations.

Below is the list of demographic variables that will be summarized.

- Age (years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Asian Indian, Black, Black African, Native Hawaiian or Other Pacific Islander, Southern African Colored, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

Below is the list of stratification factors and related screening variables.

- Country/HIV status (Peru, Philippines, South Africa and HIV positive, South Africa and HIV negative)
- TB disease severity (High severity, Low/medium severity)
- Screening smear microscopy (No AFB seen, Scanty, 1+, 2+, 3+)
- Screening Xpert semi-quantitative result (> 0 and < 18, ≥ 18) using all 5 reported Ct values

Below is the list of screening characteristics that will be summarized.

- Prior TB treatment episodes (summary statistics; categorical: none, 1 episode, ≥ 2 episodes)
- Prior TB medications used
- Recent TB Treatment history ($> 1 – 2$ years, $> 2 – 3$ years, $> 3 – 4$ years, > 4 years)
- Functional status using Karnofsky performance status score (%)
- HIV status (Positive, Negative):
  - CD4 T-cell count (cells/μL), for HIV-infected participants
- Posterior-anterior CXRs

- Normal
- Abnormal
  - Number of lung zones (≤ 2, > 2)
  - Cavitation (absent, unilateral, bilateral)
  - Size of largest cavity (0 cm, > 0 – ≤ 4 cm, > 4 cm)

Below is the list of baseline characteristics that will be summarized.

- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2) (as calculated in the database).
- Mid-upper arm circumference (MUAC) (cm)
- Baseline Xpert MTB/Rif Ultra cycle threshold

  Note: The lower cycle threshold value from any of the rpoB probes of the two sputum results will be presented. The IS1081-6110 Ct value will be ignored
- Baseline Smear microscopy

  Note: The worst of the two sputum results will be presented.
- Baseline culture status (liquid and solid)

  Note: Worst of available MGIT and LJ culture result results are considered from each participant
- Baseline Drug Susceptibility (Susceptible, Resistant, Indeterminate, Not done) for each of the following: rifampicin, isoniazid, pyrazinamide, ethambutol, bedaquiline, and delaminid
- Substance use:
  - Tobacco (never, current, former)
  - Alcohol (never, current, former)
- Baseline MGIT Time to Detection (TTD) (Days)

  Note: The lower of up to two TTDs from pure MTB-positive cultures will be presented.

NOTE: In general, baseline will be defined as the last assessment made prior to the first administered dose of trial medication. However, for sputum culture positivity and drug susceptibility testing, baseline also includes assessments through Week 1.

A data listing of demographic, baseline, and screening characteristics will be provided for the Randomized and/or Safety population.

12.3 Protocol Deviations

A summary of the frequency and percentage of participants in the Randomized population with protocol deviations (PDs) for each deviation category will be provided by treatment arm. A participant with multiple occurrences of a PD in the same deviation category (important and non-important) will only be counted once. A listing of PDs by treatment arm will be provided for all randomized participants, along with the category of deviation. The procedures for identifying and classifying PDs will be described in a PD Management Plan.

12.4 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 or later. Medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment arm for the Safety population. Summaries of SOC and PT will be sorted alphabetically by SOC and by descending frequency of PT in the 2HRZE/4HR arm. If a participant has more than 1 medical history event at a given level (eg, SOC and/or PT), the participant will only be counted once within that level. A listing of medical history for the Safety population will also be produced.

No imputation of partial or missing dates will be performed for medical history and trial days will not be presented for these cases.

TB history will include prior occurrences of TB before the ongoing TB episode under treatment in the trial. A separate TB history listing, including start and end dates of prior TB treatment episodes and TB medications taken for them, will be presented for the Safety population.

12.5 Prior and Concomitant Medications and Procedures

All medication (including vaccines, over the counter or prescription medicines, vitamins, and/or herbal supplements) taken from 30 days prior to date of signed informed consent through the last trial visit will be recorded in the appropriate section of the eCRF.

Prior and concomitant medications will be coded using the WHO Drug Dictionary (version WHO Drug September 2021 or later).

Prior medications are those with a start and end date prior to the start day of trial treatment. Concomitant medications are those with a start date or end date on or after the start day of trial treatment. If a partial start or end date allows the possibility that the medication was taken after the start of trial treatment, then the medication will be considered concomitant.

A summary by treatment for prior medications and a summary by treatment of concomitant medication will be provided for the Safety population. Additionally, a separate summary of prior and concomitant TB medications will be presented. Each summary table will report the number (%) of participants by ATC classification using ATC level 2 and medication preferred term. Participants will be counted only once within each ATC and preferred term.

All prior and concomitant medications, including prior and concomitant TB medications, will be included in a data listing. Listings will distinguish medications as prior and/or concomitant.

Concomitant procedures will be summarized by SOC and PT by treatment arm for the Safety population and will also be listed. The listing will include SOC, PT, procedure name, procedure start/end date, procedure reason, procedure location, and overall interpretation.

12.6 Treatment Adherence and Exposure

Participants will be dispensed trial drug according to the randomization schedule. The commercially marketed investigational products (delamanid, pretomanid, bedaquiline) will be packaged/repackaged in blisters or bottles as needed to support this clinical trial. The clinical stage investigational products (sutezolid and OPC-167832) will be packaged in blisters or bottles as supported by product quality data.

For each visit when treatment is dispensed and returned, drug accountability data will be integrated in the eCRF. In addition, directly observed therapy (DOT) will be required for adherence monitoring and support in all trial arms in both stages. Specific DOT models utilized, such as home visits by treatment support workers or clinic-based DOT, will be determined by prevailing national guidelines and resources available at each trial site. In addition, video observed therapy (VOT) and medication event reminder monitors, will be used to support adherence and DOT. Doses on weekends and on holidays up to 3 consecutive days may be self-administered. Details of these measures will be specified in the Trial Operations Manual. Adherence data will be collected at each trial visit during the treatment period.

A participant's treatment adherence will be summarized for the Safety Population and will be calculated separately using the two sources of information: (a) drug accountability data, and (b) exposure records captured via DOT and VOT. Summaries of treatment adherence will include descriptive statistics and categorized frequencies of % drug adherence (see Section 12.6.1.1) (< 75, ≥ 75 and < 85, ≥ 85 and < 95, ≥ 95 and ≤ 100, > 100) at Weeks 9, 11, 13, 15, 17, and, for the 2HRZE/4H treatment group, Week 26. For each time point, drug dispensed at that time point will be included in the adherence calculation.

The expected number of pills per drug to be taken is as per the dosing schedule describe in Table 1 and Table 2, a table of the actual number of pill taken for each drug and regimen will be summarized by visit and treatment arm using descriptive statistics (n, mean, SD, median, minimum, and maximum).

12.6.1 Adherence Based on Drug Accountability

Adherence based on drug accountability will rely on the information recorded on the Drug Accountability eCRF page for drug within the assigned treatment regimen. In this analysis, it will be assumed that pills not returned were taken by the participant. Calculations will not be adjusted for lost or damaged pills reported by the participant.

12.6.1.1 DBOS and PBOS Adherence

For the DBOS and PBOS regimens, adherence will be calculated for each drug in the regimen and for the overall regimen as follows:

$$\%\ \text{Adherence of drug X in regimen R for participant } i$$

$$= 100 \times \frac{\sum_{j=1}^{\text{TX\_R}(i)} [\#\text{of pills dispensed at visit } j - \#\text{of pills returned at visit } (j+1)]}{\left[\sum_{j=1}^{\text{TX\_R}(i)} (\text{expected \# of drug X pills per day}) \times [\text{visit } (j+1) \text{ date} - \text{visit } j \text{ date}] + 1\right]}$$

$$\%\ \text{Adherence of regimen R for participant } i$$

$$= \text{Average \% adherence across drugs within regimen R}$$

Where:

- Regimen R refers to DBOS or PBOS;
- Drug X refers to delamanid, pretomanid, bedaquiline, OPC-167832, or sutezolid, as applicable for a given regimen;
- $j = 1, \ldots T_{X\_R}(i)$ denotes visit j when drug X of regimen R was dispensed for participant i;
- $T_{X\_R}(i)$ denotes the total number of visits when drug X in regimen R was dispensed for participant i;
- $T_{X\_R}(i)+1$ denotes the visit after the final visit when drug X in regimen R was dispensed for participant i;
- The expected number of pills per day for each drug is shown in Table 1. For bedaquiline, the expected number will reflect the applicable dosing schedule, namely:
  - After each of the first two dispensing visits: expected number = 4 pills per day
  - From the third dispensing visit onward: expected number = 6/7 pills per day (to reflect the 2 pills thrice weekly schedule).

12.6.1.2 SOC Adherence

For the SOC regimen, adherence of the overall regimen will be calculated as follows:

$$\%\ \text{Adherence of 2HRZE/4HR for participant } i$$

$$= 100 \times \frac{\sum_{j=1}^{\text{TSOC}(i)} [\#\text{of tablets dispensed at visit } j - \#\text{of tablets returned at visit } (j+1)]}{\sum_{j=1}^{\text{TSOC}(i)} \{(\text{expected \# of tablets per day after visit } j) \times [\text{visit } (j+1) \text{ date} - \text{visit } j \text{ date} + 1]\}},$$

Where:

- $j = 1, \ldots T_{SOC}(i)$ denotes visit j when 2HRZE/4HR was dispensed for participant i;
- $T_{SOC}(i)$ denotes the total number of visits when 2HRZE/4HR was dispensed for participant i;

- $T_{SOC}(i)$+1 denotes the visit after the final visit when 2HRZE/4HR was dispensed for participant *i*;
- The expected number of tablets per day after visit *j* = number of daily FDC tablets based on weight at visit *j*, as shown in Table 2.

If SOC treatment is interrupted and dispensing changes from FDC to individual drugs within the SOC regimen, then adherence will be calculated for each drug in the SOC regimen as follows:

$$\%\ \text{Adherence of drug X in SOC regimen for participant } i$$

$$= 100 \times \frac{\sum_{j=1}^{\text{TX\_SOC}(i)}[\#\text{of pills dispensed at visit } j - \#\text{of pills returned at visit } (j+1)]}{\sum_{j=1}^{\text{TX\_SOC}(i)}\{(\text{expected \# of pills per day after visit } j) \times [\text{visit } (j+1)\ \text{date} - \text{visit } j\ \text{date} + 1]\}},$$

Where:

- $j = 1, \ldots T_{X\_SOC}(i)$ denotes visit *j* when drug X of SOC was dispensed for participant *i*;
- $T_{X\_SOC}(i)$ denotes the total number of visits when drug X of SOC was dispensed for participant *i*;
- $T_{X\_SOC}(i)$+1 denotes the visit after the final visit when drug X of SOC was dispensed for participant *i*;
- The expected number of pills per day after visit *j* = number of daily pills for drug X of SOC based on weight at visit *j*, as shown in Table 2.

If the SOC regimen for participant *i* is a hybrid of 2HRZE/4HR FDC dosing and dosing with individual drugs, then the overall SOC adherence will be calculated as the average of % adherence of 2HRZE/4HR and % adherence across individual drugs in the SOC regimen.

12.6.2 Adherence Based on Exposure Records

A participant's daily dosing information, as captured via DOT, VOT, or self-report, will be available on the exposure eCRF pages. Adherence based on exposure records for 2HRZE/4HR, DBOS and PBOS will be calculated as follows:

$$\%\ \text{Regimen adherence for participant } i$$

$$= 100 \times \frac{\text{Total \# of regimen doses actually taken}}{\text{Total \# of regimen doses expected to be taken}}$$

$$= 100 \times \frac{\sum_{j=1}^{\text{T\_R}(i)}[\#\text{of regimen doses taken between visits } j \text{ and } (j+1)]}{\sum_{j=1}^{\text{T\_R}(i)}(\text{expected \# of regimen doses per day at visit } j) + 1},$$

Where:

- Regimen refers to DBOS, PBOS, or 2HRZE/4HR;
- The *j*th dispensing of the regimen is denoted by visit *j*, $j = 1, \ldots T_R(i)$;
- $T_R(i)$ denotes the total number of visits when the regimen was dispensed for participant *i*;

- $T_R(i)+1$ denotes the visit after the final visit when the regimen was dispensed for participant *i*;
- Number of regimen doses will apply the convention described in Section 8.3.1.3 of the protocol, described below.
- Expected number of regimen doses per day at visit *j* = visit (*j*+1) date-visit *j* date.

The number of regimen doses taken between visits will be calculated by applying the following conventions:

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

In addition to the adherence summaries noted above, the number of missed regimen days will be calculated as the following difference:

> Number of missed regimen days = (total # of regimen doses expected to be taken) – (total # of regimen doses actually taken).

Summaries of the number of missed regimen days will include descriptive statistics at Weeks 9, 13, 17, and, for the 2HRZE/4HR treatment group, Week 26. For each time point, drug dispensed at that time point will be included in the adherence calculation.

12.6.3 Exposure

For each of the treatment arms, the following summaries will be presented as an overall frequency as well as over time, unless otherwise noted. Dose adjustments and reasons will be summarized for each individual drug within the regimen.

- Number of doses taken (pills)
- Percent of treated days when doses were taken within 1 hour of ingesting food
- Doses adjustment
  - Number and percentage of participants in these categories will be summarized: Dose increased, Dose reduced, Drug interrupted, Drug discontinued, Dose not changed.
- Main reason for dose adjustment
  - Adverse Event, Treatment Failure, Contraindication to trial medication(s), Other

13 EFFICACY

The efficacy analysis populations are indicated below in each section.

13.1 Definition of Unfavorable Outcome Status

Unfavorable outcome status will be derived from the Investigator's assessment for each participant throughout the treatment and follow-up periods as well as sputum culture and WGS results (see Section 11.5), and this derivation will serve as the basis for the primary efficacy endpoint and key secondary endpoints in both Stage 1 and Stage 2.

A participant will be considered to have unfavorable outcome status at Week or Month X (per Table 4 analysis visit labels) if they experience at least one of the following events. Additional details for derivation of status (unfavorable or not unfavorable) considering missing or inconclusive sputum results, are provided in Section 11.6.4.

1. Absence of microbiological cure based on a sputum sample collected at Week/Month X
   - For the Stage 1 primary endpoint, the following will be considered an unfavorable outcome:
     - DBOS/PBOS: sputum culture positive at Week 17
     - 2HRZE/4HR: sputum culture positive at Week 17 or at any subsequent time point through Week 26
     - Positive culture must be with a Mtb strain indistinguishable from baseline.
   - For additional cross-sectional analyses at time points in Stage 1 (as described in Section 13.2.3), the following will be considered an unfavorable outcome at Week X:
     - DBOS/PBOS: sputum culture positive at Week X
     - 2HRZE/4HR: sputum culture positive at Week X
     - Please refer to Table 8 with the algorithm considered when determining the microbiologically defined unfavorable outcome status at a given time point during treatment period.
2. Death from any cause.
3. Permanent discontinuation of trial treatment before the end of the assigned treatment duration for the following reasons: safety, tolerability, lack of clinical response/treatment failure, participant withdrawal, new requirement for a prohibited concomitant medication, or Investigator judgement. This includes permanent changes of trial treatment to a different TB treatment regimen for all reasons except for early trial termination. It does not include temporary interruptions permitted by the protocol.
4. For status at Week X ≥ 17 for DBOS/PBOS or Week X ≥ 26 for 2HRZE/4HR, extension of TB treatment by the Investigator more than 5 days beyond the end of the assigned treatment duration for any reason.

5. For status at Week X > 17 for DBOS/PBOS or Week X > 26 for 2HRZE/4HR, re-start of TB treatment by the Investigator during the post-treatment follow-up period excluding documented TB re-infection with a different Mtb strain than baseline.
6. Positive culture for Mtb at last visit excluding documented TB re-infection with a different Mtb strain than baseline.

As noted above, TB treatment restart in the post-treatment follow-up period and positive Mtb culture at last visit in post-treatment follow-up period will not be applicable for the Stage 1 primary efficacy endpoint, which focuses on unfavorable outcome status through end of treatment for each arm. However, both criteria will be applicable in secondary efficacy analyses evaluating 12-month post-randomization unfavorable outcome status, which will incorporate post-treatment relapse.

Because of early trial termination, some participants in the DBOS and PBOS arms did not complete the treatment regimen. In addition, participants in the HRZE arm still on-treatment at the time of early trial termination discontinued treatment within this trial and continued treatment at a local TB facility. All efficacy analyses will be conducted in trial participants who completed study treatment per protocol.

13.2 Primary Efficacy Analysis

Primary endpoint is the proportion of participants with unfavorable outcome status through end of treatment for each arm. The primary analysis will be conducted in the modified PP population.

13.2.1 Primary Efficacy Estimand

The primary estimand is defined by the following components:

Treatment:

The treatment of interest is DBOS and PBOS administered for 17 weeks versus 2HRZE/4HR administered for 26 weeks.

Population:

The modified PP population is the primary analysis population.

Participant Level Outcome:

Unfavorable outcome status at Week 17 in participants administered DBOS or PBOS

Unfavorable outcome status at Week 26 in participants administered 2HRZE/4HR

Population Level Summary:

Proportion of participants who meet the unfavorable outcome criteria for DBOS, PBOS, and 2HRZE/4HR

Intercurrent Event Strategy:

The following intercurrent events will lead to unfavorable outcome and are therefore already incorporated into the endpoint (composite strategy):

- Early treatment discontinuation for reasons defined in the protocol Section 8.3.2;
- Treatment with non-trial anti-TB medication; and

The handling of other intercurrent events is as follows:

- For participants who do not adhere to the planned treatment administration, all data will be used, irrespective of adherence. This follows a treatment policy strategy.
- Participants who become pregnant during the assigned duration of treatment will be discontinued from trial treatment and receive non-trial anti-TB treatment, which will lead to unfavorable status. This follows a composite strategy.

See Section 11.6.4 for handling of missing sputum data in the derivation of microbiologic unfavorable outcome status.

13.2.2 Primary Analysis Method

The primary efficacy endpoint in Stage 1 is the proportion of participants in the Modified PP population with unfavorable outcome status for DBOS and PBOS at Week 17 and the proportion of participants with unfavorable outcome status for 2HRZE/4HR from Week 17 through to Week 26, as defined in Section 13.1.

The unstratified difference in proportions will be presented. The originally planned analysis to adjust for stratification factors (country/HIV and TB severity) has been removed.

13.2.2.1 Whole Genome Sequencing (WGS) Data

A listing of the Whole Genome Sequencing (WGS) data will be provided, including relevant sample identifiers, sequencing quality metrics, and associated metadata. Two separate listings will be produced:

1. Lineage Listing:
    - Includes treatment information, subject ID, collection date, visit details, and lineage results.
2. SNP Differences Listing:
    - Include treatment information, subject ID, visits being compared, SNP differences, strain relatedness, and whether the record was used in unfavorable outcome assessment.

13.2.3 Cross-sectional Assessments of Unfavorable Outcome Status

In addition, unfavorable outcome status will be derived for each participant in the Modified PP population based on truncated data at the earlier milestone time points to create snapshots of unfavorable outcome rates across time for each treatment group. Due to early trial termination and limited number of participants in the modified per protocol population, unfavorable outcome status at 6 months after randomized treatment duration (10 months post-randomization for DBOS/PBOS and 12 months post-randomization for 2HRZE/4HR) will not be performed. The critical cross-sectional time points are as follows:

- Week 13 (Month 3)
- Week 17 (Month 4)
- For 2HRZE/4HR: Week 26 (Month 6)

Other cross-sectional time points may be summarized as well in tables and figures to further characterize unfavorable outcome status over time. Analysis as described above will also apply to the cross-sectional estimates, where difference in proportion unfavorable will be estimated through time. Forest plots displaying the adjusted difference in proportion unfavorable and associated 95% CIs for the key snapshot time points will also be presented.

Because unfavorable status has a composite definition, the components of the composite outcome that were met and the associated timing will be assessed and summarized individually in tables to further characterize unfavorable outcome status. The results of some components in the composite definition may become available days or weeks after a procedure was performed (eg, X-ray) or after a sample was collected (eg, sputum). In such cases, the unfavorable outcome will be attributed to the time point/visit when the associated procedure or sample collection took place. The components include the following under which the number and percentage of participants who met any of them will be summarized by the treatment arm.

- Positive culture of Mtb
- Death from any cause
- Permanent discontinuation of study regimen
- Permanent change to a different TB regimen
- Extension of TB treatment by more than 5 days beyond the end of the assigned treatment duration (if applicable)
- Re-start of TB treatment during post-treatment period excluding documented TB re-infection with a different Mtb strain from baseline (if applicable)

Unfavorable outcome status along with the specific event leading to unfavorable outcome status at selected visits will be presented in bar plots by visit and detailed in a listing.

13.2.4 Supplementary Estimands and Sensitivity Analyses

The following populations will also be evaluated as supplementary estimands for the primary efficacy analysis:

- Supplementary analysis I: A supplementary analysis will be conducted by repeating the primary analysis described in Section 13.3.2 in the Modified PP population. Participants in all arms with definitive results showing susceptibility to rifampicin and/or isoniazid at baseline will be included in the analysis.
- Supplementary analysis II: A supplementary analysis will be conducted by repeating the primary analysis described in Section 13.2.2 in the Modified PP population with the condition that participants in the 2HRZE/4HR will be considered to have unfavorable outcome status based on the absence of microbiological cure if they have a positive sputum culture at Week 26 (instead of the primary definition for which a sputum culture positive at Week 17 or at any subsequent time point through Week 26 would be considered an unfavorable outcome).
- Supplementary analysis III: A variation of the first supplementary analysis will be conducted, except that only participants in the 2HRZE/4HR treatment arm with definitive results showing susceptibility to rifampicin and/or isoniazid at baseline will be included in the analysis.

The following sensitivity analyses will be conducted.

- Sensitivity analysis I: A sensitivity analysis of the primary analysis will be conducted by considering an MTB-positive sputum culture at the evaluated time point as unfavorable, regardless of strain (ignoring whole genome sequencing).
- Sensitivity analysis II: To assess the possible impact of missing data to the primary results, the primary analysis described in Section 13.2.2 will be repeated for EOT (unfavorable outcome status at Week 17 for DBOS and PBOS and from Week 17 through Week 26 for 2HRZE/4HR) and 12-month post-randomization time point in the Modified PP population. Participants with imputed data (based on Table 10 in Section 11.6.4) at these time points will be assumed to have an unfavorable outcome status.

A participant listing will be presented indicating which of the sensitivity and supplementary analysis they were included in.

13.3 Secondary Efficacy Analyses

13.3.1 Unfavorable Outcome Status at 6 Months After Randomized Treatment Duration

Due to early trial termination, this secondary efficacy endpoint will not be assessed.

13.3.2 Unfavorable Outcome in HIV Co-Infected Participants

Due to early trial termination and low enrollment in this sub-population, this secondary efficacy endpoint will not be assessed.

13.3.3 Sputum Culture Conversion (SCC)

Sputum Culture Conversion (SCC) will be derived based on up to 6 culture results per timepoint, if all are available. SCC at a timepoint (ie, Week X) is defined as two negative cultures obtained at least 5 days apart, up to and including Week X, without any intervening or subsequent positive culture results (through Week X), ignoring contaminated and unevaluable cultures. SCC will be analyzed in the Modified PP population.

For the confirmatory analysis of SCC by EOT and SCC by Week X, dates will be used instead of visit labels. Specifically, for SCC at Week X, the last study day within the visit window (Table 4) for Week X will serve as the backstop date. For example, SCC at Week 9 will include all culture results collected on or before Day 71, while SCC at Week 15 will include all results on or before Day 113, and so on.

The frequency and percentage of participants achieving SCC will be presented for the following timepoints for all arms: Week 9, Week 15, Week 19, and End of Treatment (EOT). SCC at EOT will be evaluated at Week 19 for DBOS/PBOS and at Week 28 for HRZE.

Liquid Culture (MGIT) SCC will be determined using the individual MGIT culture results as detailed in Table 5, and the visit-level culture result derivation as outlined in Table 6.

Solid Culture (LJ) SCC will be determined by the derivation of LJ culture results as described in Table 5 and derivation of visit culture result described in Table 6.

For Composite Cultures SCC will be determined using a combination of up to 6 results (2 MGIT and 4 LJ cultures) derived from Table 5 and Table 6, with the visit-level culture result derivation detailed in Table 7.

Ideally, 6 culture results (2 MGIT + 4 LJ) are expected at each assessment through Week 28, and 4 culture results (2 MGIT + 2 LJ) for visits at Month 7 and later. However, on 21 June 2024, laboratories were advised to discontinue diluted LJ cultures for visits occurring after Week 28. As a result, only 4 culture results are expected for these visits occurring after this date, comprising 2 MGIT and 2 LJ results.

If fewer than 6 culture results for visits through Week 28 or fewer than 4 culture results for visits at Month 7 and later are available, the following checks will be performed:

- If the missing sample result does not have an inoculation date, the result is considered missing.
- If the inoculation date is available but the result is not, the result is considered missing.

- If any positive culture result is present among the available results, the composite result for that visit will be considered positive.

- If no positive result is found, the derived composite culture result for the visit will be classified as unevaluable.

Swimmer plots displaying each participant's culture results throughout the treatment period will also be presented for each culture type (MGIT, solid, composite) and detailed in individual listings.

13.3.4 Sustained Sputum Culture Conversion Based on MGIT Culture, Solid Culture, and Composite Culture Results

Below are the 3 definitions of sustained sputum culture conversion (SSCC) to be used for the time to SSCC (tSSCC) analyses. Note: "successive" refers to two chronologically adjacent results, ignoring unevaluable results between those two results.

- SSCC1 is defined as two successive Mtb culture negative results, collected at least 5 days apart, without *any intervening or subsequent* Mtb culture positive result for the duration of a participant's follow-up. For Mtb culture positive results at or after Week 17, the strain must be indistinguishable from baseline based on WGS to lose SSCC status.

- SSCC2 is defined as two successive Mtb culture negative results, collected at least 5 days apart, without *two or more consecutive* MTB positive culture results at least 5 days apart without an intermediary negative culture result for the duration of follow-up, regardless of strain.

- SSCC3 is defined as two successive Mtb culture negative results, collected at least 5 days apart (*regardless of any subsequent MTB positive culture results* that occur during a participant's follow-up).

Note that the SSCC algorithm will consider sample collection dates rather than visit windows.

13.3.5 Time to Sustained Sputum Culture Conversion Based on MGIT Culture, Solid Culture, and Composite Culture Results

Time to sustained sputum culture conversion (tSSCC) based on MGIT culture results is defined as the time from first dose to the first of two successive Mtb culture negative results, collected at least 5 days apart without an intervening Mtb culture positive result. Time to SSCC will be analyzed in the Modified PP and PP populations. Participants in the Modified PP population who never achieve SSCC will be censored at the date of sputum collection that yielded their last negative or positive culture result. Participants in the PP population who never achieve SSCC will be censored at the date of treatment discontinuation due to early trial termination. Time to SSCC will be analyzed using a Cox proportional hazards model to compare DBOS to 2HRZE/4HR and PBOS to 2HRZE/4HR.

The calculation of tSSCC will be based on the actual sample collection dates rather than assigned visit windows. This approach allows for a more precise use of available data and prevents missing or contaminated results from being prioritized simply due to their proximity to a planned visit day.

Sensitivity analysis will also be conducted in the Modified PP population considering alternative definitions of time to sustained SCC as defined (SSCC2 and SSCC3) in Section 13.3.4 above.

The Cox proportional hazards model will include fixed effect terms for treatment arm, country/HIV status, and TB disease severity. The Cox-model estimate of the log-hazard ratio and its standard error will be used to construct a model-based estimate of the confidence limits on the HR. The confidence limits are first constructed for the log HR and then exponentiated to provide the corresponding confidence limits on the HR scale. In case of ties in reporting event times, the Efron option in the SAS procedure PHREG will be used. The hazard ratios for DBOS and PBOS relative to 2HRZE/4HR and associated 95% CIs will be presented in a summary table.

The assumption of proportional hazards will be tested using the proportional hazards test based on the Schoenfeld residuals and by reviewing the log minus log survival plot (against log time) after fitting the Cox proportional hazards model. Alternative methods (eg, restricted mean survival time) will be considered if proportionality does not hold.

Time to SSCC will be analyzed using the Kaplan-Meier method. Kaplan-Meier (KM) time to SSCC curves for each treatment arm will be presented graphically and median time (displayed in weeks) to conversion along with the respective 95% CI will be estimated. KM estimates at the key milestone time points (ie, 9, 13, 17, and 26 weeks) with associated 95% CIs will be summarized. Because procedures and sample collections may occur slightly later than these time points, the KM estimates associated with each of these time points will be based on the upper limit of the corresponding visit window as defined in Table 4.

Summaries of the number and percentage of participants experiencing an event, participants censored (overall and by reason for censoring) will be provided along with median (and 95% CI) time of SSCC (displayed in weeks) for each treatment group. Bar plots displaying the proportion of participants with SSCC on MGIT, Solid, and Composite Cultures at end of study from each treatment arm will also be presented.

A listing will be produced, including whether the participant had the event or, date of event/censored date, the start date, and the time to event (days).

13.3.6 MGIT Sputum Culture Time to Detection

MGIT sputum culture time to detection (TTD) will be analyzed in the modified PP population to characterize the rate of change in days to detection through Weeks 4, 9, 13, and EOT (Week 17 for XBOS, Week 26 for HRZE). TTD will be measured as the length of time (days) from the beginning of culture incubation to the detection of bacterial growth, and will only be assessed from a pure Mtb-positive culture. Since for each visit up to two MGIT cultures will be performed, the shorter time to detection from the (up to) 2 results with at least one pure Mtb-positive (ie, the individual raw lab culture result is “Positive for MTB Complex” without

contamination and without NTM) per timepoint will be used in the analysis. When TTD for a pure Mtb-positive culture is not concluded by day 42 (ie, > 42 days), the value will be defined to be 43 days. When a MGIT culture is reported as "Negative for MTB Complex", the TTD will be imputed to 43 days. If culture results are "Positive for MTB Complex with contamination", "Positive for MTB and NTM", "Contaminated", or "No result", they will be excluded from the analysis.

A summary statistics table for the TTD (days) will be presented for the following timepoints: baseline, Week 4, Week 9, Week 13, and EOT (Week 17 for XBOS, Week 26 for HRZE) displaying the actual and change from baseline summaries by the treatment arms.

The endpoint will be the change from baseline in the TTD (days) to week T (BA_{TTD}[0-T]), ie, average change in TTD (days) per week over T weeks, denoted BA_{TTD}(0-T). In order to estimate the average change in TTD (days) per week from baseline to week T, a linear mixed effects model will be used with average change from baseline of TTD (days) as the outcome and fixed effects for treatment and time (week), baseline TTD (days), along with an interaction between treatment and time. The model will also be adjusted by TB disease severity and Country/HIV contingent on sufficient sample sizes in all of the strata.

The model is given by the following.

$$TTD\ (days)\ = \alpha + u_i + (\beta_1 + b_i)t + \beta_{2j}X_{1j} + \beta_{3j}X_{1j}t + \beta_4 X_{2i} + \varepsilon_{ij}$$

where $t = 1, 2 \ldots, T$, X_{1j} is the dummy indicator for treatments $j = 1,2$ with HRZE as the reference group, X_{2i} the covariate for baseline TTD (days), u_i the random intercepts with distribution $u_i \sim N(0, \sigma_u^2)$, b_i the random slopes with distribution $b_i \sim N(0, \sigma_b^2)$ and $\varepsilon_{ij} \sim N(0, \sigma^2)$.

An unstructured covariance structure will be used for the variance-covariances of the random effects. It may be simplified to variance components (option "vc") if the former doesn't yield convergence or there is no gain in model fit as decided through the AIC.

Estimated least square means for each treatment arm and the associated 95% CI will be presented for Weeks 4, 9, 13, and EOT (Week 17 for XBOS, Week 26 for HRZE).

13.3.7 Anti-TB Drug Resistance

The emergence of resistance to delamanid, bedaquiline, isoniazid, rifampicin, pyrazinamide, and ethambutol will be assessed through classic drug susceptibility testing using critical concentrations using MGIT. MIC testing will be performed separately for pretomanid, sutezolid, OPC-167832, bedaquiline, and delamanid. These results will be summarized separately for classic susceptibility testing and MIC testing, by looking at baseline susceptibility to each tested drug in the Modified PP population and any shift to resistance post baseline as well as change in MIC (if any). If multiple MIC values exist for a particular participant, the highest MIC value will be summarized in the shift table.

Separate listings for classic drug susceptibility test results per visit and MIC test results per visit will be presented for the PP population.

13.4 Subgroups

Primary analysis (described in Section 13.2.2) will be repeated for the following subgroups in the Modified PP population.

- Sex
- Age Group (< 30, 30-49, > 49)
- Race (Black, Nonblack)
- Country (South Africa, Philippines)
- Baseline visit smear findings (1-2+, 3+, TNTC)
- Note: The worst of the two sputum results will be presented.
- Cavitation (Absent, Unilateral, Bilateral)
- Baseline visit Xpert MTB/RIF Ultra cycle threshold (< 18, ≥ 18)

  Note: The lower cycle threshold value from any of the rpoB probes of the two sputum results will be presented. The IS1081-6110 Ct value will be ignored

13.5 Interim Analysis for Stage 1

The planned interim analysis, originally intended to assess the treatment-shortening potential of DBOS and PBOS after all Stage 1 participants completed treatment (17 weeks for DBOS and PBOS and 26 weeks for 2HRZE/4HR), will no longer be conducted. As a result of early trial termination (described in Section 5), the Stage 1 analyses as described in the current revised SAP will serve as the final analysis.

14 MORTALITY

A table summarizing the number and percentage of participants in the Safety population who died within each treatment arm during the trial will be presented. The table will include the following death details:

- Overall number and percentage of deaths
- Number and percentage of each primary cause of death (TB, HIV, and Others: Specify)
- Number and percentage of deaths that were violent or non-violent
- Number and percentage of the associated adverse events
- Whether autopsy was performed or not

A listing of the death details will also be provided indicating date of death, primary cause, associated AE, whether death was violent or non-violent and whether autopsy was performed.

15 SAFETY AND TOLERABILITY

Safety and tolerability of the combination regimens of DBOS and PBOS administered for 17 weeks compared to 2HRZE/4HR administered for 26 weeks will be evaluated through a number of safety measures including assessment of severe AEs (Grade 3) and serious AEs (SAEs) through minimally 2 weeks after the end of treatment (primary) and the end of the post treatment follow up period (12 months post randomization). Additionally, all-cause permanent trial treatment discontinuation will be evaluated.

Vital signs, ECGs, physical examinations, visual examinations, peripheral neuropathy assessment, functional status and clinical laboratory tests will be conducted at scheduled visits during the treatment and post treatment follow-up period.

Subgroup analyses by HIV are no longer planned due to the small number of HIV-infected participants.

15.1 Adverse Events

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

Each verbatim AE term will be coded to a SOC and PT using the most recent version of the MedDRA dictionary Version 24.1 or later. Intensity for each AE will be graded using Division of Allergy and Infectious Diseases (DAIDS) grading as Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially Life-threatening), or Grade 5 (Death), as determined by the Investigator and recorded on the eCRF.

If the start date of an AE is incomplete or missing, the event will be assumed to be started after trial day 1, unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicates that the event started before trial day 1.

Treatment-emergent AEs (TEAEs) are new or worsening AEs that start on or after first dose of treatment and no later than 2 weeks after last dose of treatment. TEAEs will be considered to be related to trial regimen if the TEAE is related to any of the individual trial drugs within the regimen. In addition to a listing of TEAEs, an additional listing of AEs that occurred after informed consent and prior to start of trial treatment will be produced.

In this trial the following AEs will be reported as AESI:

- Hepatotoxicity, defined by all the following:
  - Elevated ALT or AST > 3x ULN,
  - Elevated total bilirubin > 2x ULN,

  - Any preferred terms within the following SOCs that the Investigator classifies as "AESI" on the eCRF
    - Hepatobiliary SOC
    - Investigations SOC
  - No evidence of cholestasis (not programmable), and
  - No reasonable alternative explanation than drug-induced liver injury for the elevation in ALT/AST and total bilirubin, such as viral hepatitis (not programmable)
- Peripheral neuropathy: Peripheral neuropathy of severity Grade 3 or above (SMQ: peripheral neuropathy)
- Optic neuropathy: Optic neuritis confirmed by an ophthalmologist (SMQ: optic neuropathy)
- Hematologic toxicity: Grade 3 or above anemia, leukopenia, or thrombocytopenia (based on laboratory measures and/or adverse events)
- Cardiotoxicity: QTcF interval prolongation > 500 msec or a clinically significant cardiac arrhythmia associated with QT prolongation, such as Torsades de pointes or polymorphic ventricular tachycardia (based on ECG and/or "Torsade de Pointes/QT Prolongation" SMQ)

A TEAE overview table containing the frequency and percentage of participants as well as number of reported events through 2 weeks after the end of treatment in each of the following categories (summarized by treatment group) will be presented in the Safety Population. In addition, for each category, separate tables will be summarized by treatment arm, SOC and PT for the Safety Population.

- Any TEAEs
- Any TEAEs related to trial regimen
- Any Severe AE (≥ Grade 3)
- Any Severe AE (≥ Grade 3) related to trial regimen
- Any Serious TEAEs
- Any Serious TEAEs related to trial regimen
- Any TEAEs of special interest (AESI)
- Any treatment-emergent AESIs related to trial regimen
- Any TEAEs leading to permanent trial treatment discontinuation
- Fatal TEAEs

Summaries of SOC and PT will be sorted alphabetically by SOC and by decreasing frequency of preferred term in the overall Safety population (then alphabetically for ties). If a participant has more than one TEAE at a given level (SOC or preferred term), the participant will only be counted once within that level. For participants with more than one episode of the same event, the maximum severity grade and maximum relationship to each trial drug will be considered. An

AE that is related to any of the individual drugs within a regimen will be considered to be related to the trial regimen.

An AE listing by participant will display all reported AEs up to end of Follow-up visit or the Early Withdrawal visit and will include the verbatim term in addition to the SOC and preferred term. This listing will also include all relevant data associated with the event: eg, date of onset, date resolved, severity, whether it is serious, outcome, relationship to trial drug, action taken with each trial drug, and whether it's due to overdose of the trial drug. When a date is presented, the trial day associated with the date will also be displayed.

Separate listings for the following will be provided:

- Listing of all AEs per participant
- Listing of all AEs in participants co-infected with HIV at baseline
- Listing of participants with Serious TEAEs
- Listing of participants with TEAEs leading to trial treatment discontinuation
- Listing of participants with TEAEs of special interest (AESI)
- Listing of participants with TEAEs leading to death

The secondary safety analyses to assess the safety and tolerability of the combination regimens of DBOS and PBOS administered for 4 months compared to 2HRZE/4HR will consider AEs under the following conditions:

- AEs occurring through 12 months post-randomization
- All-cause trial treatment discontinuation
- Severe AE (≥ Grade 3) and SAEs in each arm through the end of the post treatment follow up period (12 months post randomization)

Separate tables for the above categories will be summarized by treatment arm, SOC and PT summarizing the frequency and percentage of participants who experienced at least 1 TEAE. For computing percentages, the denominator is the number of participants in the Safety population for the given treatment arm or, as applicable, the number of HIV-infected participants in the treatment arm.

The following will be summarized by treatment arm and AESI category during the treatment period.

- Day of onset of TEAESIs
    - Descriptive statistics (N, mean, SD, median, minimum, maximum) will be presented for the days of AE onset. This will be calculated as (AE start date – Treatment start date +1) in days.
- Duration of TEAESIs
    - Descriptive statistics (N, mean, SD, median, minimum, maximum) will be presented for the AE duration. End date for AEs still ongoing at end of trial will be set to participant's end of study date.

- Number of TEAESIs reported per participant
    - Count of all reported AE events for each participant will be summarized. Multiple records for the same PT based on change in grade and/or action taken will be considered a continuous event and counted once based resolution date or designation of "ongoing" at the time of analysis.

15.2 Clinical Laboratory

Clinical laboratory values for hematology, and serum chemistry at baseline (screening) and each post-baseline visit, including changes from baseline will be summarized by treatment arm using descriptive statistics (n, mean, SD, median, minimum, and maximum).

Summaries by DAIDS toxicity grade and graded shift tables will be used to summarize hematology and serum chemistry laboratory values by visit and treatment group. Additionally, shift from baseline to worst case post-baseline toxicity grade will also be summarized. For the by time point summary, the denominator for the proportion is the number of participants with non-missing values at baseline and the given time point in the treatment group for the given lab parameter.

Creatinine toxicity grading shift table summaries will account for the following 3 considerations:

1. Actual Values Table: This table will summarize creatinine toxicity grades based solely on actual values.
2. Relative to Baseline Table: This table will summarize grades based only on values relative to baseline.
3. Summary Table: This table will integrate both criteria—actual values and relativity to baseline—presenting the higher grade between the two.

All laboratory test results will be listed. The listings will include date and trial day of collection. All units will be displayed in System International units. Out of reference ranges values will be flagged in the data listings (eg, Low as 'L' or High as 'H').

For female of childbearing potential, pregnancy testing will be done at the scheduled time points. Summary of the result (positive, negative) and specimen type (urine, serum) will be presented over time by treatment group. A listing of the results will also be presented.

15.3 Hepatoxicity

Participants with at least one of the following liver abnormalities will be summarized using the following categories. Percentages will be based on participants with data available post-baseline for each parameter.

- alanine transaminase (ALT) or aspartate transaminase (AST) > 8x ULN or ALT/AST > 5x screening value or > 500 U/L (whichever occurs first) if screening ALT/AST was > 1.5x ULN

- ALT/AST > 5x ULN for > 2 weeks or ALT/AST > 3x screening value or > 300 U/L (whichever occurs first) if screening ALT/AST was > 1.5x ULN
- ALT/AST > 3x ULN and total bilirubin > 2x ULN or international normalized ratio (INR) > 1.5 or ALT/AST > 2x screening value or > 300 U/L (whichever occurs first) if screening ALT/AST was > 1.5x ULN AND (total bilirubin > 2 x ULN OR INR > 1.5).
- ALT/AST > 3x ULN and clinical symptoms/signs of hepatitis (fatigue, anorexia, nausea, vomiting, right upper quadrant pain/tenderness, hepatomegaly, jaundice, and/or dark urine) or a systemic hypersensitivity reaction (fever, rash, and/or eosinophilia [> 5%]) or ALT/AST > 2x screening value or > 300 U/L (whichever occurs first) if screening ALT/AST was > 1.5x ULN
    - Clinical signs and symptoms of hepatitis will be defined through the MedDRA terms in Table 12 below.

Table 11. MedDRA Terms to Define Hepatitis

Description Term	Preferred Term	High Level Term
Fatigue	Fatigue	
Anorexia	Decreased appetite	
Nausea	Nausea	
Vomiting	Vomiting	
Right upper quadrant pain	Abdominal pain upper	
Hepatomegaly	Hepatomegaly	
Dark urine	Chromaturia	
Systemic hypersensitivity	Hypersensitivity	Allergies to foods, food additives, drugs and other chemicals
	Drug hypersensitivity	Allergic conditions NEC

A drug-induced liver injury (DILI) listing will be created for participants meeting the criteria above.

Participant meeting Hy's Law criteria at least once post-baseline will be summarized and also listed in a by-participant listing:

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

The proportion of participants meeting any of the individual criteria above will also be summarized. In addition, profile plots of ALT, AST, total bilirubin, and ALP will be produced for participants who meet any of the first 3 criteria above.

Plots to support evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be produced by treatment group, which are scatterplots of the following hepatic laboratory parameters.

- Total bilirubin peak (y-axis) vs. ALT peak (x-axis), where the peak values are shown as multiples of ULN for the respective parameter. These plots will include a vertical dashed line at 3 × ULN for ALT and a horizontal dashed line at 2 × ULN for total bilirubin. The upper right quadrant is the Hy's law range and represent potential Hy's law cases;
- Total bilirubin peak (y-axis) vs. AST peak (x-axis), where the peak values are shown as multiples of ULN for the respective parameter. These plots will include a vertical dashed line at 3 × ULN for AST and a horizontal dashed line at 2 × ULN for total bilirubin.

Additionally, an eDISH listing showing the individual results and the quadrants for ALT, AST, and TBL will be presented.

The following example plot is taken from Chalasani and Regev (2016).

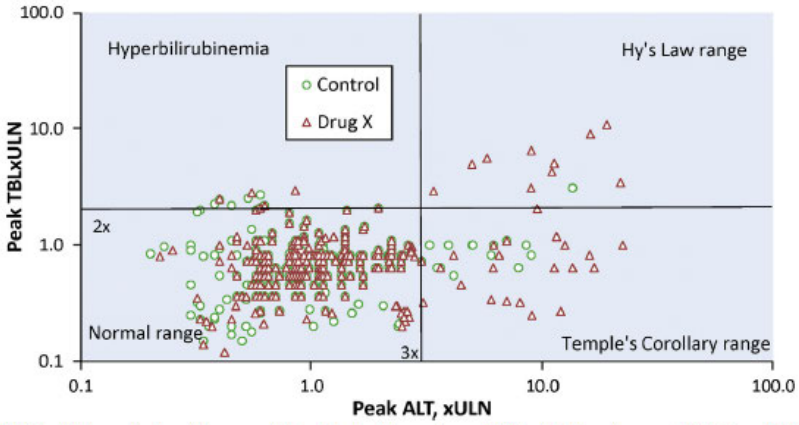


Figure 1. An eDISH plot in patients with normal liver tests at baseline. eDISH plot showing peak ALT and TBL levels from a database of a phase III clinical trial. The peak serum ALT is shown along the x-axis, and the peak serum TBL is shown along the y-axis as multiples of the ULN on log scales. Over-representation of points on the study drug in the Hy's law range quadrant and the Temple's corollary range quadrant suggests a possible increased risk of severe DILI. ALT, alanine amino-transferase; DILI, drug-induced liver injury; eDISH, Evaluation of Drug-Induced Serious Hepatotoxicity; TBL, total bilirubin; ULN, upper limit of normal.

15.4 Electrocardiograms

QT interval and corrected QT interval by Fridericia (QTcF) measured at Screening, Weeks 2, 4, 9, 13, 17, 21, 26, and Month 12 and changes from baseline will be listed and summarized using descriptive statistics by treatment arm and presented in boxplots. Since the ECGs will be performed in triplicate, for summaries the average of the triplicate assessments will be used.

Potentially clinically important criteria for QTcF are defined as follows:

- Observed: 451 to 480, 481 to 500, and > 500 msec

For each of the criteria, the frequency and proportion (expressed in percent) of participants who met the criterion at each time point will be provided by treatment arm. For the by time point summary, the denominator for the proportion is the number of participants in the treatment arm

with non-missing values at baseline and the given post-baseline time point. A boxplot of QTcF measurements by visit and treatment arm will also be presented.

A listing of participants with at least one potentially clinically significant QTcF interval value will also be provided.

15.5 Vital Signs

Vital signs (temperature, heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP], oxygen saturation, respiratory rate [RR], mid-upper arm circumference, weight, and body-mass index [BMI]) will be measured at each visit while sitting or in supine position. Values at each visit and changes from baseline will be listed and summarized by treatment group using descriptive statistics and presented in boxplots.

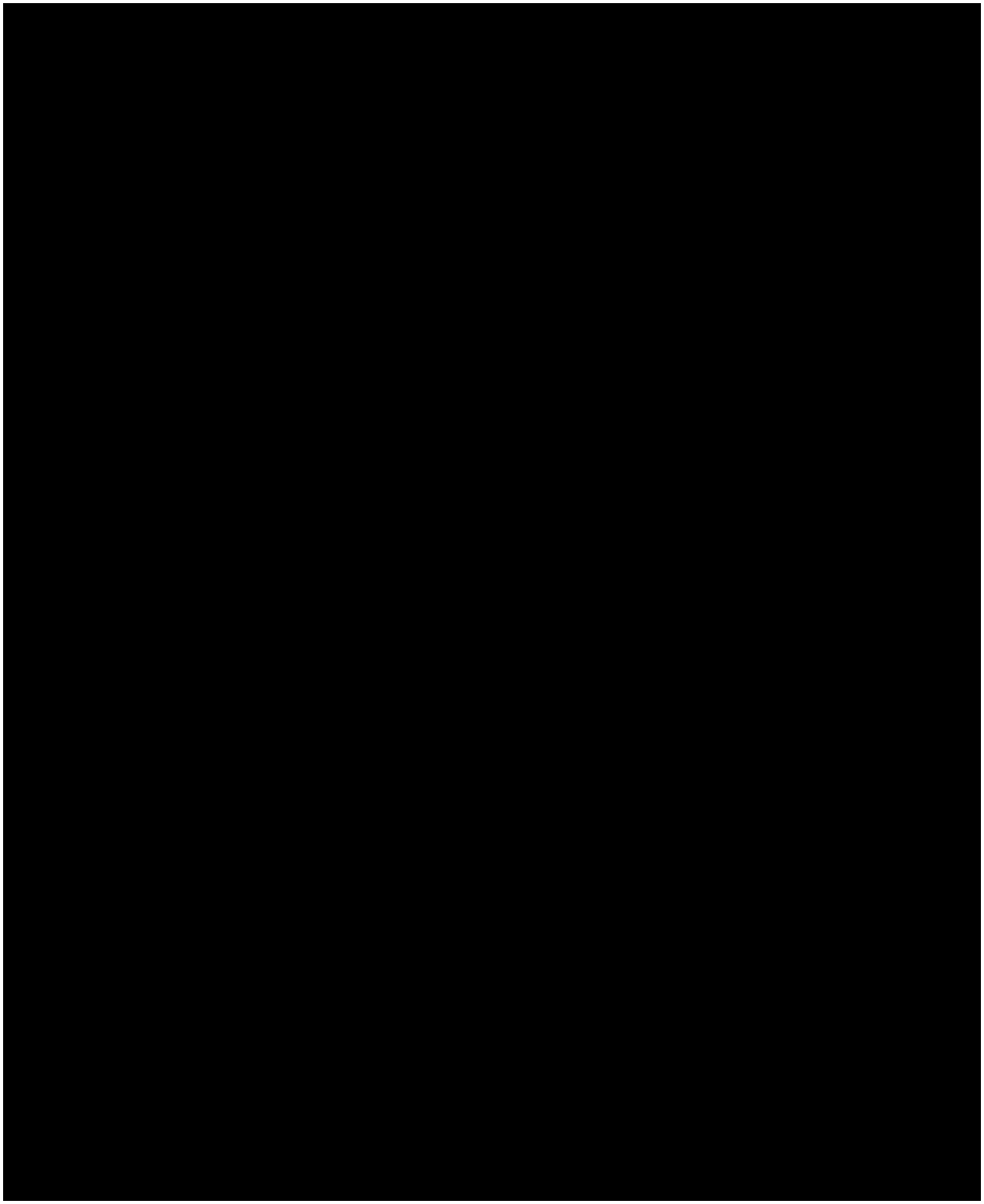
A listing of participants with at least one post-baseline clinically important criterion vital sign will be presented.

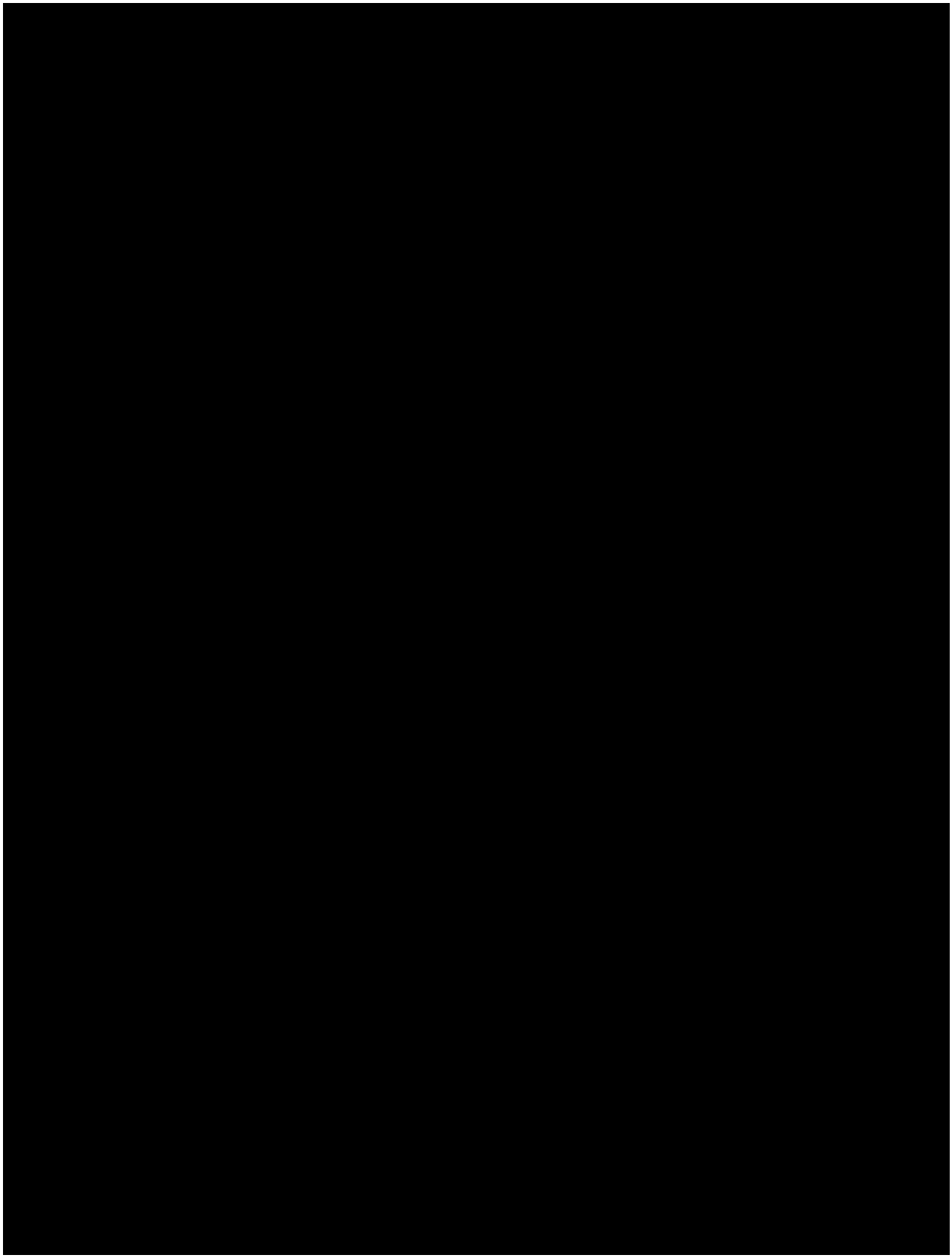
15.6 Physical Examinations

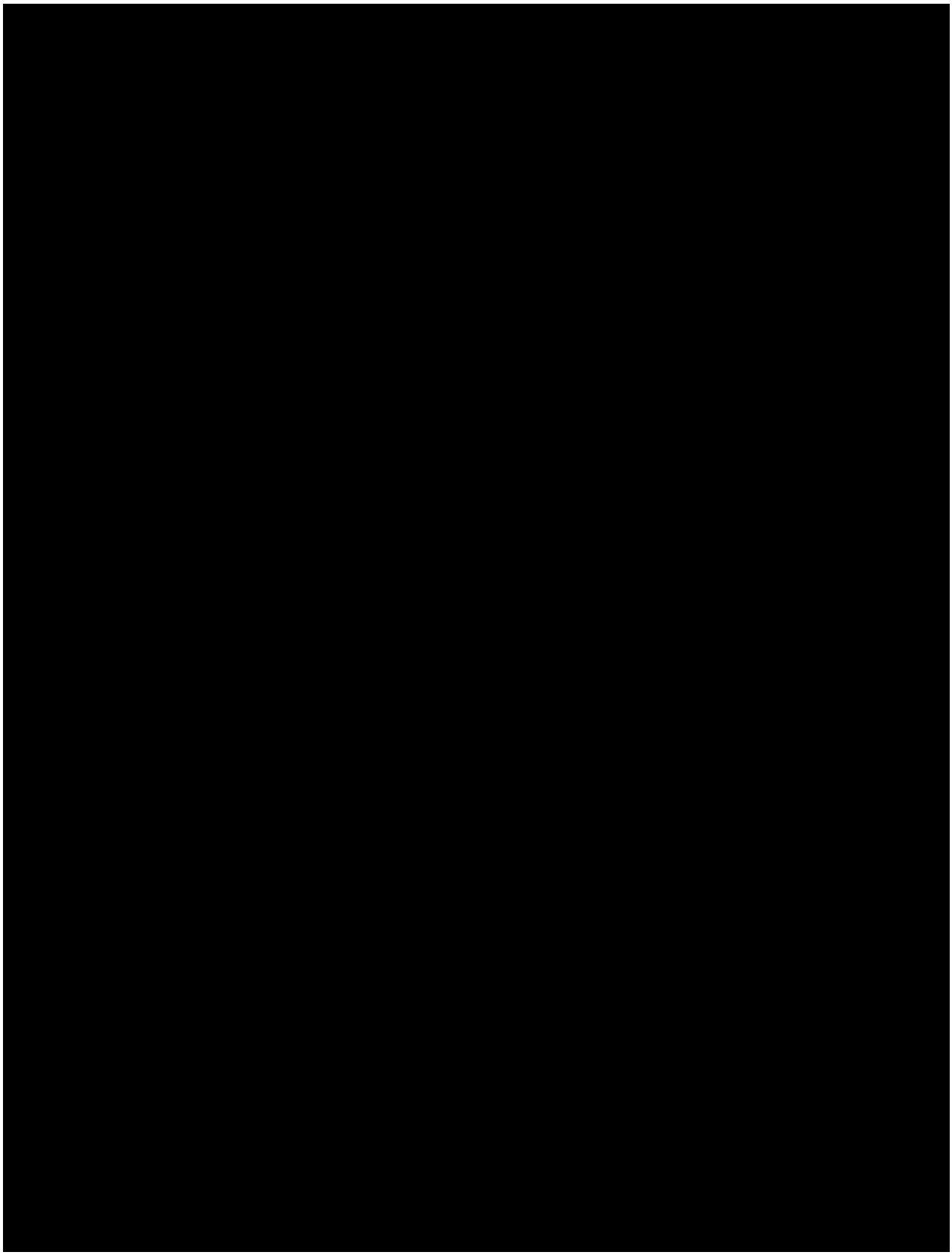
Physical examination results will be listed only.

16 EXPLORATORY ANALYSES

The Safety population will be used for all exploratory analyses described in this section.







17 Pharmacokinetics

Sparse PK sampling for each drug in the regimen will be performed for all participants in the experimental arms (DBOS and PBOS) only of both Stage 1 and 2. Population PK analysis will be used to analyze PK characteristics of delamanid and its metabolite DM-6705, bedaquiline and its metabolite M2, OPC-167832, pretomanid, and sutezolid and its metabolite PNU-101603.

A separate PK SAP will address the planned analyses to support the PK and DDI objectives.

18 References

Chalasani N, Regev A. Drug-Induced Liver Injury in Patients with Preexisting Chronic Liver Disease in Drug Development: How to Identify and Manage? Gastroenterology 2016; 151:1046-1051.

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Mohamed K, Embleton A, Cuffe RL. Adjusting for covariates in non-inferiority studies with margins defined as risk differences. Pharmaceutical statistics 2011; 10(5): 461-466.

19 Appendices

19.1 Appendix 1 Schedule of Assessments

See protocol for Schedule of Assessments.

19.2 Appendix 2 Imputation of Partial Dates

Table 12. Imputation Rules for Partial Dates – Adverse Events

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y are prior to first trial drug dose	First day of indicated month
		M and Y is same as first trial drug dose	Date of first trial drug dose
		M and Y are after first trial drug dose	First day of indicated month
	M and D	Y is prior to first trial drug dose	01 Jan of indicated year
		Y is same as first trial drug dose	Date of first trial drug dose
		Y is after first trial drug dose	01 Jan of indicated year
	M, D, and Y	-	Date of first trial drug dose
End Date	D only	M and Y are prior to last trial drug dose	Last day of indicated month
		M and Y is same as last trial drug dose	Date of last observation
		M and Y are after last trial drug dose	First day of indicated month
	M and D	Y is prior to last trial drug dose	31 Dec of indicated year
		Y is same as last trial drug dose	Date of last observation
		Y is after last trial drug dose	01 Jan of indicated year
	M, D, and Y	-	Date of last observation
	-	Estimated end date is before a complete or imputed AE start date	Last day of the month of AE start date

D = day; M = month; Y= year.
Note: The imputation of end date must be later than start date

Table 13. Imputation Rules for Partial Dates – Prior and Concomitant Medications

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y same as M and Y of first trial drug dosing	Date of first trial drug dose
		M and/or Y not the same as M and Y of first trial drug dosing	First day of indicated month
	M and D	Y same as Y of first trial drug dosing	Date of first trial drug dose
		Y not the same as Y of first trial drug dosing	01 Jan of indicated year
	M, D, and Y	none – date completely missing	Date of first trial drug dose
End Date	D only	M and Y same as M and Y of last trial drug dosing	Date of last trial drug dose
		M and/or Y not the same as M and Y of last trial drug dosing	Last day of indicated month
	M and D	Y same as Y of last trial drug dosing	Date of last trial drug dose
		Y not the same as Y of last trial drug dosing	31 Dec of indicated year
	M, D, and Y	none – date completely missing	Date of last trial drug dose

D = day; M = month; Y= year.

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