Approvals

A5362

Primary Statistical Analysis Plan

Version 3.0

A Phase IIc Trial of Clofazimine- and Rifapentine-Containing Treatment Shortening Regimens in Drug-Susceptible Tuberculosis: The CLO-FAST Study

Protocol Version 2.0 and LOA #1

ClinicalTrials.gov Identifier: NCT04311502

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Version History

Version	Changes Made	Date Finalized
1	Original Version (protocol v1.0, LOA #1, LOA #2)	6/2/2021
1.1	Minor version update for LOA #3. No changes necessary.	February 1, 2022
2.0	Revised to align with protocol v2.0 and CM #1.	January 10, 2023
3.0	• Revised to align with protocol v2.0 and LOA #1 • Details added to reflect early close to accrual and data that will contribute to the primary analysis report • Revisions to analysis specifications for time to event outcomes • Additional details added for some outcome measures for clarity • Edits throughout to remove redundant or duplicated information • Updated writing team members and statisticians	October 13, 2023

Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and key secondary estimands and other outcome measures that will address specific study objectives and interim monitoring of the A5362 study. The Primary SAP includes general approaches for all primary estimands, key secondary estimands, and other outcome measures in the primary manuscript(s) or submitted to ClinicalTrials.gov (regardless of the reporting timeline). The Primary SAP facilitates discussion of the statistical analysis components among the lead study investigators and statisticians, helping them agree on the statistical analyses to be performed and presented in the primary analysis report.

Detailed outlines of tables, figures, and coding descriptions that will be included in the primary analysis report are included in the Analysis Implementation Plan (AIP). Outlines of analyses for the exploratory objectives and exploratory outcome measures (which we do not describe in the Primary SAP) are provided in a separate SAP.

2 Study Overview

2.1 Overview of Study Design

A5362 is an open-label, randomized phase IIc study to evaluate whether a 3-month regimen of rifapentine/isoniazid/pyrazinamide/ethambutol (PHZE) with clofazimine (CFZ) dosed as 100 mg daily with a 2-week 300 mg daily loading dose is superior to the standard of care (SOC) 6-month regimen of rifampin/isoniazid/pyrazinamide/ethambutol (RHZE) for DS-TB with respect to (1) early bacteriologic efficacy defined as time to culture conversion by 12 weeks post-randomization and (2) safety over 65 weeks.

Participants will be randomized to one of three treatment arms; Arm 1 with treatment for 13 weeks (including a 2-week CFZ loading dose of 300 mg daily; Arm 2 with treatment for 26 weeks; or Arm C with treatment for 4 weeks with an experimental regimen and the remaining 22 weeks with SOC (PK subgroup)).

- Arm 1 (Experimental): PHZE + CFZ 300 mg once daily for 2 weeks, PHZE + CFZ 100 mg once daily for 6 weeks; then PHZ + CFZ 100 mg once daily for 5 weeks
- Arm 2 (SOC): RHZE for 8 weeks; then RH for 18 weeks
- Arm C (PK subgroup): PHZE + CFZ 100 mg once daily for 4 weeks; then on study, off study medications and treated according to SOC (RHZE for 4 weeks; RH for 18 weeks)

We will follow all participants in Arms 1, 2, and C from randomization to week 65 for the primary and secondary objectives. Protocol v2.0 LOA #1 also includes extended follow-up for some participants corresponding to new exploratory objectives which will be detailed in a separate SAP.

Participants who consent to intensive PK sampling visits will be randomized to Arms 1, 2, or C in a 2:1:1 ratio, respectively, while participants who do not consent to intensive PK sampling will be

randomized only to Arms 1 or 2 in a 2:1 ratio, respectively. We will stratify randomization based on HIV status and the presence of advanced disease as determined by chest X-ray. We will balance randomization by institution.

The primary efficacy analysis will be a superiority comparison of time to liquid culture conversion through 12 weeks in Arm 1 compared with Arm 2. The primary safety analysis will estimate and compare the proportions of participants who have a Grade 3 or higher safety event that is at least one grade higher than baseline at any time during the study. Important secondary analyses include 65-week favorable composite efficacy outcome, including cumulative relapse proportion versus 6-month SOC controls; and safety and tolerability (regimen discontinuation) in Arms 1 and 2.

The primary completion date for A5362 is the final visit date that is included in the primary safety analysis, which will occur approximately 65 weeks after the last participant enrolls. With the early closure to accrual in June 2023, the primary analysis report forming the basis of the primary manuscript will occur earlier than the original planned timepoint. We will prepare the primary analysis report using data collected at visits up to and including the date when the last enrolled participant completes the week 26 study visit. We will later conduct a supplemental analysis using data through week 65, which will form the basis of a secondary manuscript and the clinicaltrials.gov requirements.

2.2 Hypotheses

A 3-month regimen of rifapentine/isoniazid/pyrazinamide/ethambutol (PHZE) with clofazimine (CFZ) dosed as 100 mg daily with a 2-week 300 mg daily loading dose (Arm 1) will demonstrate early efficacy (time to 12-week liquid culture conversion) relative to standard of care (SOC) (RHZE; Arm 2), and will have acceptable safety and tolerability.

2.3 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol. We address other study objectives outlined in the protocol in subsequent secondary analysis plans.

We will analyze the primary efficacy objective below (2.3.1.1) using a superiority framework based on a one-sided 0.05 alpha level test. For analyses of other objectives, we will present estimates of the parameter of interest alongside their respective two-sided confidence intervals, as specified in Section 5.

We will finalize all analyses for the primary analysis report once the last enrolled participant has completed the week 26 study visit and all queries have been resolved.

2.3.1 **Primary Objectives**

2.3.1.1 To compare time to 12-week liquid culture conversion for Arm 1 with Arm 2 (SOC controls).

2.3.1.2 To compare the proportion of adverse events (safety) over 65 weeks between Arm 1 and Arm 2 (SOC controls).

2.3.2 **Secondary Objectives**

Each is a comparison between Arm 1 and Arm 2 unless otherwise specified.

2.3.2.1 To compare proportion of participants who experience a favorable composite efficacy outcome at 65 weeks between Arm 1 and Arm 2 participants

2.3.2.2 To compare premature regimen discontinuation (tolerability) between Arm 1 and Arm 2 participants

2.3.2.3 To estimate and compare CFZ-associated increases in QT interval (QTcF, using the Fridericia correction)

2.3.2.4 To estimate and compare time to stable liquid and solid mycobacterial culture conversion

2.3.2.5 To compare proportion of participants with liquid and solid culture conversion at weeks 8 and 12 between Arm 1 and Arm 2 participants

2.3.2.6 To compare days to positivity in automated liquid mycobacterial culture over treatment time

2.3.2.7 To compare chest radiographic score (with specific attention to resolution of cavitary disease) between Arms from baseline to end of treatment (Arm 1, week 13; Arm 2, week 26) between Arm 1 and Arm 2 participants

2.3.2.8 To compare proportions of participants who experience a favorable clinical/bacteriologic treatment outcome at 65 weeks between Arm 1 and Arm 2 participants

2.3.2.9 To estimate cumulative relapse and recurrence proportions up to week 65 for participants on Arm 1 and Arm 2

2.3.2.10 To determine CFZ pharmacokinetic (PK) parameters in plasma in Arm 1

2.3.2.11 To compare PK parameters when CFZ is given with a loading dose in Arm 1 and without a loading dose in Arm C

2.3.2.12 To objectively and subjectively assess CFZ-associated skin hyperpigmentation between Arm 1 and Arm 2 participants

2.4 Overview of Sample Size Considerations

We plan to enroll a total of 185 participants; approximately 110 in Arm 1, 55 in Arm 2, and 20 in Arm C. We estimate that we will have at least 90% power to detect an effect between Arm 1 and Arm 2 with respect to the primary efficacy outcome. We assume 70% culture conversion by week 12 in Arm 2 and a hazard ratio of 1.8. We use a 2:1 allocation ratio and assume that 10% of participants will have unevaluable culture conversion results.

For the primary safety outcome, we will compare proportions of participants with any Grade 3 or higher adverse events (AE) between Arms. Table 10.4-2 from the study protocol (copied below) gives the power we would have to detect that Arm 1 is inferior to Arm 2 assuming a two-sided type 1 error of 0.10, 10% probability of developing an AE in the SOC Arm, and varying probabilities (15-30%) of developing an AE in experimental Arm. We also provide the 90% confidence interval (CI) width for the comparison.

Protocol Table 10.4-2

Power	N1	N2	N	Arm 1 Proportion with ≥Grade 3 AE	Arm 2 Proportion with ≥ Grade 3 AE	Two-sided type 1 error	90% CI Width
0.13	100	50	150	0.15	0.10	0.10	0.210
0.36	100	50	150	0.20	0.10	0.10	0.218
0.64	100	50	150	0.25	0.10	0.10	0.225
0.85	100	50	150	0.30	0.10	0.10	0.230

2.5 Overview of Formal Interim Monitoring

The Data and Safety Monitoring Board (DSMB) will perform an initial review of the study between 4-6 months after the first enrollment, and thereafter at least every 6 months or on another schedule requested by the DSMB. For all reviews, we will provide the DSMB with detailed information on safety, tolerability, and administrative aspects (including accrual, retention, and compliance with study requirements).

There was one planned interim analysis for futility of the primary efficacy outcome using a conditional power approach. This analysis was to be conducted once 50% of participants had reached week 12 of follow-up. However, due to the early close to accrual, this interim analysis will not be completed.

3 Outcome Measures

3.1 Primary Outcome Measures

3.1.1 Early Efficacy

Time to stable culture conversion in liquid media, defined as the first of two (consecutive or non-consecutive) negative sputum cultures without an intervening positive culture, and/or visits wherein the participant is unable to produce sputum and has no signs of active TB, up to 12 weeks post-randomization.

3.1.2 Safety

Proportion across study arms experiencing any Grade 3 or higher AE that is at least a one-grade increase from baseline over 65 weeks

3.2 Secondary Outcome Measures

3.2.1 Composite Efficacy

A: Proportion with favorable clinical/bacteriologic outcome at 65 weeks post randomization

B: Proportion with favorable composite outcome including treatment completion at 65 weeks post-randomization.

Favorable, unfavorable, and unevaluable clinical/bacteriological outcomes (A) are defined as follows:

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

- Participants with liquid culture negative status at week 65.
- Participants without signs or symptoms of ongoing active TB and are unable to produce a sputum specimen at 65 weeks.
- Participants who at the end of the follow-up period are clinically without symptoms/signs of ongoing active TB and produce a sputum specimen that is contaminated in two liquid cultures without evidence of TB.

For any of the above to be considered favorable, participants must not already have been considered unfavorable, as defined below.

Unfavorable Outcome

- Absence of cure. A participant will be considered to have absence of bacteriological cure if a sputum sample obtained at or after end of treatment for Arm 1 (week 13), or at or after week 17 for Arm 2 is culture-positive in liquid or solid media for an *Mtb* strain genotypically matched with the initial isolate. A second sputum sample, obtained at least four hours following the first sputum collection (see section 6.2.3 of protocol), is required to confirm absence of bacteriological cure.
- Participants who die from any cause during study treatment or follow-up except from violent or accidental cause (e.g., road traffic accident).

- Participants who had a positive culture for *Mtb* when last seen, whether confirmed by a second sample or not, unless determined to have been re-infected.
- Participants experiencing extension of treatment beyond the nominal level (week 13 for Arm 1 and week 26 for Arm 2) due to clinically inadequate response. These cases should be managed individually in conjunction with and after having notified the A5362 Clinical Management Committee (CMC). Extension of treatment to make up missed doses will not count as unfavorable.

Unevaluable Outcome

- Participants lost to follow-up during treatment or post-treatment follow-up with their last culture being negative for *Mtb*.
- Violent or accidental death.
- Participants with recurrent TB due to a new strain of *Mtb* confirmed by conventional molecular genotyping (as defined by MIRU and IS6110 typing).
- Women who become pregnant during their assigned active treatment and stop their assigned treatment.

Favorable, unfavorable, and unevaluable composite outcomes (B) are defined as follows:

Favorable Outcome
Same as in outcome measure 3.2.1 A.

Unfavorable Outcome
Same as in outcome measure 3.2.1 A, and:

- Participants lost to follow-up during treatment phase of each Arm (i.e., 13 weeks and 26 weeks for Arms 1 and 2, respectively).
- Participants failing to complete treatment (see below for Definitions of Adequate Treatment) and not assessable at the end of the follow-up period.
- Participants receiving any one or more of the following:
  - extension of treatment beyond the nominal level, except to make up missed doses
  - a re-start of treatment following ≥30 consecutive days lost to follow-up
  - a change in at least one drug in treatment regimen for any reason except re-infection, pregnancy, or temporary drug challenge.

Unevaluable Outcome

- Participants lost to follow-up after treatment phase, and not assessable at the end of follow-up, with their last culture being negative for *Mtb.*
- Violent or accidental death.
- Participants re-infected with a new strain of *Mtb* confirmed by conventional molecular genotyping (as defined by MIRU and IS6110 typing).
- Women who become pregnant during their assigned active treatment and stop their assigned treatment.

Definitions of Adequate Treatment Within 3-month Regimen (Arm 1)

- Taken a total of at least 56 doses of allocated intensive phase treatment within 70 days of starting treatment
- AND taken at least 28 doses of continuation phase treatment within 49 days (7 weeks) of completion of the intensive phase
- AND missed no more than 21 doses of medication overall.

Definitions of Adequate Treatment within 6-month Regimen (Arm 2)

- Taken a total of at least 56 doses of allocated intensive phase treatment within 70 days of starting treatment
- AND taken at least 100 doses of continuation phase treatment within 154 days (22 weeks) of completion of the intensive phase
- AND missed no more than 42 doses of medication overall.

3.2.2 Tolerability

Proportion with premature discontinuation through 65 weeks, defined as discontinuation other than due to violent death, natural disaster, or administrative censoring.

3.2.3 QT interval

We derive the outcome measures defined below from ECG readings, which the site conducts in triplicate (three ECGs 5-10 minutes apart). We will use the mean of all measurements (up to 3) that are readable and available.

3.2.3.1 Mean baseline QTcF and change from baseline in mean QTcF at weeks 2, 8, and end of treatment (EOT) (Arm 1, week 13; Arm 2, week 26)

3.2.3.2 Occurrence of absolute QTcF ≥480 ms and <500 ms, and ≥500 ms, at any time during study treatment

3.2.3.3 Occurrence of QTcF change from baseline of ≥30 ms and <60 ms, and ≥60 ms, at any time during study treatment

3.2.4 Time to stable culture conversion in liquid and solid media through week 65

Defined as the first of two (consecutive or non-consecutive) negative sputum cultures without an intervening positive culture, and/or visits wherein the participant is unable to produce sputum and has no signs of active TB. Conducted separately for liquid and solid media.

3.2.5 Proportion of participants with culture conversion at weeks 8 and 12 across all study arms.

Liquid (MGIT) and solid media analyzed separately.

3.2.6 Time (days) to positivity in liquid culture (MGIT) after start of treatment through week 65

We will report the median (Q1, Q3) times to positivity in liquid culture at each time point (weeks 1, 2, 3, 4, 6, 8, 10, and 12) in Arm 1 and Arm 2.

3.2.7 Change in chest X-ray (CXR) score from baseline to end of treatment (EOT).

Sites conduct the baseline chest X-ray during screening. We will compute the chest X-ray score with the following validated formula (Ralph et al. Thorax 2010):

CXR Score = percent of total lung affected by any pathology + 40 (if cavitation is present).

We will compute the CXR scores based on both site assessment of the chest X-ray and an assessment by independent central reviewers blinded to study treatment.

3.2.8 Proportion of participants with one or more serious adverse events (SAEs) through week 65

3.2.9 Proportion of participants who have a TB relapse from EOT until week 65

For participants who had successful culture conversion through the end of study treatment, TB relapse is defined as a recurrence of TB emanating from the same strain as the participant's originally diagnosed TB, which will be determined through molecular genotyping.

3.2.10 Proportion of participants who have a TB recurrence from EOT until week 65

3.2.11 Plasma pharmacokinetic parameters for CFZ

Arm 1

We will report the minimum concentration (Cmin), maximum concentration (Cmax), time of Cmax (Tmax), and area under the concentration curve (AUC0-24h) estimated though non-compartmental analysis for weeks 2 and 13 summarized separately.

Arm C

We will report the estimated minimum concentration (Cmin), maximum concentration (Cmax), time of Cmax (Tmax), and area under the concentration curve (AUC0-24h) estimated though non-compartmental analysis for week 2.

Arm 1 versus Arm C

We will compare the estimated minimum concentration (Cmin), maximum concentration (Cmax), time of Cmax (Tmax), and area under the concentration curve (AUC0-24h) at week 2 between Arm 1 and Arm C intensive PK participants. We will estimate the geometric mean ratio comparing Arm 1 to Arm C and corresponding 90% confidence interval. As a supplemental analysis, we will use a Wilcoxon rank sum test and report the p-value.

3.2.12 Change from baseline in skin pigmentation (colorimetric L*, a*, b* parameters) utilizing ambient light-independent reflectance mapping at weeks 8, 13, 26, and 65.

Mean change in total color difference from week 0 to each of weeks 8, 13, 26, 65 in Arm 1 vs Arm 2 at each of the following locations; (1) left cheek, (2) right cheek, (3) forehead, (4) chin.

Mean change in total color difference from week 0 to each of weeks 8, 13, 26, 65 in Arm 1 vs Arm 2 using, for each participant, the location with the maximum change.

3.2.13 Change from baseline in participant-reported changes in skin pigment and distress related to perceived skin hyperpigmentation at weeks 8, 13, 26, and 65.

Mean subjective 'change in coloration' score between week 0 and weeks 8, 13, 26, and 65 in Arm 1 vs Arm 2 (10-point numeric rating scale where 0=none, 10=most significant possible).

Mean subjective 'distress related to skin coloration' score at each of weeks 0, 8, 13, 26, and 65 in Arm 1 vs Arm 2 (10-point numeric rating scale where 0=none, 10=worst possible)

4 Statistical Principles

4.1 General Considerations

All statistical comparisons described in Section 3 are between Arms 1 and 2, unless otherwise noted. The analysis set or study population is specified for the analysis of each study objective. We explicitly define these in the next section.

For time-to-event analyses, we will base each participant's follow-up time from the date of randomization. We will compute the time to event as the weeks from randomization to the study visit week when the event occurred, not the actual date of the visit. Similarly, participants who do not have an event by the last scheduled visit and are not lost to follow-up are censored on the respective study visit week, not the actual date of their last visit. This ensures there are not major artificial fluctuations in the risk set near the end of the period for the outcomes in which we estimate Kaplan-Meier proportions at a fixed time point.

For analyses where we estimate Kaplan-Meier proportions at a fixed time point, we will use Greenwood's estimator to estimate the variance of the proportions in each arm, and the variance for the difference in proportions between arms will be computed as the sum of the squared variance estimates for Arms 1 and 2.

4.1.1 Analysis set definitions

4.1.1.1 Analysis sets (used for primary (5.1.1) and key secondary (5.1.2) estimands):

- Efficacy Set:
  All participants who are randomized to study treatment and are not late exclusions. (Participants will be late exclusions if they do not have any positive culture (liquid or solid) at screening, entry, or week 1, or if they have TB that is RIF-resistant or INH-resistant identified at screening or entry.)

- Safety Set:
  All participants who start assigned study treatment.

- Start treatment/not late exclusion set:
  All participants who start assigned study treatment and are not late exclusions.

- Alive/adequate treatment set:
  All participants who complete an adequate course of treatment as defined within Sections 10.2.5 and 10.2.6 of the protocol and who do not die during treatment.

- Per protocol Set:
  All participants who start and complete assigned study treatment.

4.1.2 Subgroups of interest

Subgroups defined by levels of sex
Subgroups defined by levels of race/ethnicity
Subgroups defined by levels of HIV status
Subgroups defined by presence (or absence) of advanced disease on chest x-ray conducted at screening.

4.1.3 Interim Monitoring

4.1.3.1 Early Assessment of QT Prolongation

After 12 Arm 1 participants have evaluable AE data through week 2, we will find the point estimate of the proportion of participants in the ITT population on Arm 1 with prolonged QT interval (defined by QTcF > 500 ms) and corresponding two-sided Pearson-Klopper exact 95% confidence interval.

4.1.3.2 Interim Futility Analysis

Note: Due to the early closure to accrual, this analysis will not be conducted.

We will estimate the conditional power of the test statistic at the second DSMB review using two methods in the efficacy set.

1) Under the assumption that the future data follows the hypothesized difference between Arm 1 and Arm 2 (hazard ratio of 1.8 between arms).

2) Under the assumption that future data follows the estimated difference between Arm 1 and Arm 2 at the time of the review (the estimated hazard ratio).

4.1.3.3 **Unfavorable Composite Outcome Monitoring in Arm 1**

We will find the two-sided 95% confidence bands for cumulative unfavorable outcome probabilities in Arm 1 in the safety set approximately one month after the first participant completes treatment, and will continue approximately monthly and for each DSMB review until the end of the study. We will present these estimates alongside historical unfavorable proportions for SOC on the REMox, OFLOTUB, RIFAQUIN, and Study31 trials, and A5362 SOC data as available. There will be no adjustment to the confidence bands for multiple looks.

4.1.3.4 **Early Recurrence Monitoring in Arm 1**

We will find the two-sided 95% confidence bands for cumulative relapse probabilities in Arm 1 beginning approximately 2 months after the first participant completes treatment, and will continue approximately monthly and for each DSMB review until the end of the study. We will present these results alongside historical relapse proportions for SOC on the REMox, OFLOTUB, and RIFAQUIN trials, and A5362 SOC data as available. There will be no adjustment to the confidence bands for multiple looks.

5 Analysis Approaches

5.1.1 Primary Estimands

<table>
<tr><th colspan="3">Primary Objective 2.3.1.1: To compare time to 12-week liquid culture conversion for Arm 1 with SOC controls (Arm 2)</th></tr>
<tr><td>Estimand description</td><td colspan="2">Time to liquid culture conversion through 12 weeks of follow-up among individuals aged ≥18 years and with pulmonary TB without demonstrated isoniazid or rifampicin resistance.</td></tr>
<tr><td>Treatment</td><td colspan="2">13-week Experimental Regimen:
rifapentine/isoniazid/pyrazinamide/ethambutol (PHZE) + clofazimine (CFZ)

26-week Standard of Care:
rifampicin/isoniazid/pyrazinamide/ethambutol (RHZE) followed by rifampicin/isoniazid (RH)</td></tr>
<tr><th>Target population</th><th colspan="2">Analysis set</th></tr>
<tr><td>Individuals aged ≥18 years living with confirmed pulmonary TB without demonstrated isoniazid or rifampicin resistance.</td><td colspan="2">Efficacy set (All participants who are randomized to study treatment and are not late exclusions)</td></tr>
<tr><th>Variable</th><th colspan="2">Outcome measure 3.1.1</th></tr>
<tr><td>Time to stable culture conversion based on sputum samples taken at serial collections up to 13 weeks after treatment initiation.

Note: The time of stable culture conversion will be the time of the sampling date of the first of two culture negative sputum samples in liquid media (MGIT) without an intervening positive culture. We also consider a participant’s inability to produce sputum with no signs of active TB at a given visit as a negative sputum culture. A negative culture at week 13 can be used as the confirmatory second culture to determine stable culture conversion at week 12.</td><td colspan="2">Time to stable culture conversion in liquid media, defined as the first of two (consecutive or non-consecutive) negative sputum cultures without an intervening positive culture, and/or visits wherein the participant is unable to produce sputum and has no signs of active TB, up to 12 weeks post-randomization.</td></tr>
<tr><th>Handling of intercurrent events</th><th colspan="2">Handling of missing data</th></tr>
<tr><td>The following intercurrent events are relevant to the estimand:

1. Failure to start TB treatment
Observations will be used to determine the variable (treatment policy strategy)

2. Premature treatment discontinuation due to suspected TB treatment failure or TB recurrence or poor treatment response.
Observations will be used to determine the variable (treatment policy strategy)

3. Premature TB treatment discontinuation due to TB death
Observations will be used to determine the variable (treatment policy strategy)

4. Premature treatment discontinuation for other reason
Observations will be used to determine the variable (treatment policy strategy)

5. Non-TB death</td><td colspan="2">Participants who have contaminated or missing samples leading up to and including week 12 will be censored at the last sampling date for which they had a valid sputum culture assessment.

Participants who experience premature TB treatment discontinuation due to TB death will be censored at week 12.</td></tr>
</table>

Observations will be used to determine the variable (treatment policy strategy)	
Population-level summary measure	Analysis approach
Hazard ratio of culture conversion through 12 weeks of follow-up.	We will estimate the treatment effect with a hazard ratio and corresponding 90% two-sided confidence interval. We consider Arm 1 superior to Arm 2 if the one-sided p-value is less than 0.05 in favor of Arm 1. The hazard ratio (HR) will be estimated from a Cox proportional-hazards model, with HIV status (positive; negative) and advanced disease according to chest X-ray (yes/no) treated as stratification factors. We will assess the proportional hazards assumption visually by plotting the scaled Schoenfeld residuals against the natural logarithm of the time to event. In the event that the data violate the proportional hazards assumption, we will conduct the primary analysis with a stratified log-rank test. Participants who do not achieve stable culture conversion, but who are on study and have contaminated or missing cultures leading up to and including week 12 will be censored at the last sampling visit for which they had a valid sputum culture assessment. Participants who are lost to follow-up prior to 12 weeks with their last culture being positive will be censored at 12 weeks (i.e. assumed they did not have a culture conversion by week 12), and participants who are lost to follow-up prior to 12 weeks with their last culture being negative will be censored at the last sampling visit for which they had a valid culture result. Participants who die prior to week 12 will be censored at 12 weeks.

Sensitivity Analyses

None.

Supplemental Analyses

We will also test the treatment by sex and treatment by race/ethnicity interaction terms in separate Cox proportional hazards models. These models will also include the same stratification factors as the primary analysis: HIV status and advanced disease according to chest X-ray reading. In a supplemental analysis, we will estimate the difference in restricted mean survival times (difference in restricted mean time to culture conversion) for a time horizon of 12 weeks.

<table>
<tr><th colspan="3">Primary Objective 2.3.1.2: To compare the proportion of adverse events (safety) over 65 weeks between Arm 1 and Arm 2</th></tr>
<tr><td>Estimand description</td><td colspan="2">Probability of having at least one grade 3 or higher adverse event through 65 weeks that is at least a one-grade increase from baseline among patients aged ≥18 years living with pulmonary TB without demonstrated isoniazid or rifampicin resistance.</td></tr>
<tr><td>Treatment</td><td colspan="2">13-week Experimental Regimen:
rifapentine/isoniazid/pyrazinamide/ethambutol (PHZE) + clofazimine (CFZ)

26-week Standard of Care:
rifampicin/isoniazid/pyrazinamide/ethambutol (RHZE) followed by rifampicin/isoniazid (RH)</td></tr>
<tr><th>Target population</th><th colspan="2">Analysis set</th></tr>
<tr><td>Patients aged ≥18 years living with pulmonary TB without demonstrated isoniazid or rifampicin resistance who initiate TB therapy.</td><td colspan="2">Safety Set (All participants who start their assigned study treatment)</td></tr>
<tr><th>Variable(s)</th><th colspan="2">Outcome measure 3.1.2</th></tr>
<tr><td>Occurrence of a Grade 3 or higher adverse event through 65 weeks that is new in onset or aggravated in severity of frequency from the baseline condition.</td><td colspan="2">Proportion across study arms experiencing any Grade 3 or higher AE that is at least a one-grade increase from baseline over 65 weeks.</td></tr>
<tr><th>Handling of intercurrent events</th><th colspan="2">Handling of missing data</th></tr>
<tr><td>1. Persistent clinical disease and extension of treatment
Observations will be used to determine the variable (treatment policy strategy)

2. Premature treatment discontinuation
Observations will be used to determine the variable (treatment policy strategy)

3. Premature treatment discontinuation due to suspected TB treatment failure or TB recurrence or poor treatment response.
Observations will be used to determine the variable (treatment policy strategy)</td><td colspan="2">Participants who discontinue follow-up before week 65 will have their outcome determined based on data available until the time of discontinuation (i.e., missing observations after discontinuation that would be relevant to the variable are considered missing completely at random).

Sensitivity analyses will consider participants who discontinue follow-up before week 65 as having at least one Grade 3 or higher adverse event that is at least a one-grade increase from baseline.</td></tr>
<tr><th>Population-level summary measure</th><th colspan="2">Analysis approach</th></tr>
<tr><td>Probability of having at least one Grade 3 or higher AE that is at least one-grade increase from baseline at any time during the 65 weeks after treatment initiation.</td><td colspan="2">We will compare the cumulative proportion of participants experiencing a Grade 3 or higher AE that is at least one-grade increase from baseline at any time during the 65-week study period between Arm 1 and Arm 2 using the Kaplan-Meier estimator at week 65. Participants who have not experienced an event will be censored at the last completed study visit. For participants who experience more than one event, we will use the time of the first occurrence as the time of event. We will present the point estimate and 90% two-sided confidence intervals for the difference in cumulative proportions.</td></tr>
</table>

Supplemental Analyses:

As supplementary analyses, we will also estimate the Kaplan-Meier proportions and confidence intervals for the outcome measure up to week 13, and up to week 26. These time horizons correspond to the end of treatment for Arm 1, and Arm 2, respectively.

5.1.2 Secondary Estimands

<table>
<tr><td colspan="2">Secondary Objective 2.3.2.1:
To compare proportions of participants treated with RPT/CFZ-containing regimens who experience favorable composite efficacy outcome at 65 weeks with Arm 2 (6-month SOC controls)</td></tr>
<tr><td>Estimand description</td><td>Difference in proportion with favorable outcomes 65 weeks after initiation of TB therapy (PHZE+CFZ versus RHZE) among individuals aged ≥18 years and with pulmonary TB without demonstrated isoniazid or rifampicin resistance.</td></tr>
<tr><td>Treatment</td><td>13-week Experimental Regimen:
rifapentine/isoniazid/pyrazinamide/ethambutol (PHZE) + clofazimine (CFZ)

26-week Standard of Care:
rifampicin/isoniazid/pyrazinamide/ethambutol (RHZE) followed by rifampicin/isoniazid (RH)</td></tr>
<tr><td>Target population</td><td>Analysis set</td></tr>
<tr><td>Individuals aged ≥18 years with confirmed pulmonary TB without demonstrated isoniazid or rifampicin resistance who initiate TB therapy.</td><td>Efficacy set (All participants who are randomized to study treatment and are not late exclusions)</td></tr>
<tr><td>Variables</td><td>Outcome measure 3.2.1 A</td></tr>
<tr><td>Favorable outcome 65 weeks after initiation of TB therapy following evidence of cure at treatment completion where favorable outcome is defined by any one of the following:

• Liquid culture negative at 65 weeks after TB therapy initiation

• No signs or symptoms of ongoing active TB and unable to produce a sputum specimen at 65 weeks after TB therapy initiation

• No signs or symptoms of ongoing active TB and a sputum specimen that is contaminated in two liquid cultures without evidence of TB at 65 weeks after TB therapy initiation

Absence of cure at or after treatment completion is an unfavorable outcome.</td><td>Favorable clinical/bacteriologic outcome at the 65 week study visit.</td></tr>
<tr><td>Handling of intercurrent events</td><td>Handling of missing data</td></tr>
<tr><td>The following intercurrent events are relevant to the estimand.

1. Death except from violent or accidental cause (e.g., road traffic accident)
Unfavorable outcome (composite strategy)

2. Violent or accidental death
Unevaluable outcome* (hypothetical strategy)

3. Extension of treatment beyond the nominal duration due to clinically inadequate response
Unfavorable outcome (composite strategy)

4. New TB diagnosis due to a new strain of Mtb
Unevaluable outcome* (hypothetical strategy)</td><td>Participants lost to follow-up and culture negative at their last visit meet the definition of “unevaluable” and will be censored at the time of their last follow-up visit

Participants with a positive culture for Mtb when last seen, whether confirmed by a second sample or not, unless determined to have been re-infected will be considered to have an unfavorable outcome and the event time will be the visit when last seen.

Participants with a new TB diagnosis due to a new strain of Mtb will be censored at the time of their last follow-up visit.</td></tr>
</table>

5. Pregnancy during treatment resulting in discontinuation of initial therapy Unevaluable outcome* *(hypothetical strategy)* 6. Failure to complete treatment (except for 2 and 5 above) *All follow-up through to 65 weeks will be used to determine the variable irrespective of duration of treatment (treatment policy strategy)* * See handling of missing data for imputation rules for unevaluable outcomes	Participants who become pregnant during assigned active treatment and discontinue treatment will be censored at the time of treatment discontinuation.
Population-level summary measure	Analysis approach
Difference in cumulative probability of having a favorable clinical/bacteriologic outcome at 65 weeks after TB therapy initiation.	Difference in cumulative proportion of participants at 65 week visit together with 90% and 95% two-sided confidence intervals. We will use the Kaplan-Meier estimator and Greenwood's estimate for the standard error.

<table>
<tr><td colspan="3">Secondary Objective 2.3.2.1:
To compare proportions of participants treated with RPT/CFZ-containing regimens who experience favorable composite efficacy outcome at 65 weeks with Arm 2 (6-month SOC controls)</td></tr>
<tr><td>Estimand description</td><td colspan="2">Difference in proportion favorable outcomes 65 weeks after initiation of TB therapy (PHZE+CFZ versus RHZE) among individuals aged ≥18 years and with pulmonary TB without demonstrated isoniazid or rifampicin resistance who complete TB treatment.</td></tr>
<tr><td>Treatment</td><td colspan="2">13-week Experimental Regimen:
rifapentine/isoniazid/pyrazinamide/ethambutol (PHZE) + clofazimine (CFZ)

26-week Standard of Care:
rifampicin/isoniazid/pyrazinamide/ethambutol (RHZE) followed by rifampicin/isoniazid (RH)</td></tr>
<tr><td>Target population</td><td colspan="2">Analysis set</td></tr>
<tr><td>Individuals aged ≥18 years living with confirmed pulmonary TB without demonstrated isoniazid or rifampicin resistance who complete TB therapy.</td><td colspan="2">Efficacy set (All participants who are randomized to study treatment and are not late exclusions)</td></tr>
<tr><td>Variables</td><td colspan="2">Outcome measure 3.2.1B</td></tr>
<tr><td>Favorable outcome 65 weeks after initiation of TB therapy following evidence of cure at treatment completion where favorable outcome is defined by any one of the following:

• Liquid culture negative at 65 weeks after TB therapy initiation

• No signs or symptoms of ongoing active TB and unable to produce a sputum specimen at 65 weeks after TB therapy initiation

• No signs or symptoms of ongoing active TB and a sputum specimen that is contaminated in two liquid cultures without evidence of TB at 65 weeks after TB therapy initiation

Absence of cure at or after treatment completion is an unfavorable outcome.</td><td colspan="2">Favorable clinical/bacteriologic outcome at the 65 week study visit.</td></tr>
<tr><td>Handling of intercurrent events</td><td colspan="2">Handling of missing data</td></tr>
<tr><td>The following intercurrent events are relevant to the estimand:

Intercurrent events that occur during therapy:

1. Death except from violent or accidental cause (e.g., road traffic accident)
Unfavorable outcome* (Composite strategy)

2. Violent or accidental death
Unevaluable outcome* (Composite strategy)

3. A re-start of therapy following ≥ 30 consecutive days without therapy
Unfavorable outcome (Composite strategy)

4. A change in at least one drug in treatment regimen for any reason except re-infection, pregnancy, or temporary drug challenge.
Unfavorable outcome (Composite strategy)</td><td colspan="2">Participants lost to follow-up during the treatment phase are considered to have an unfavorable outcome (regardless of TB culture result at the last available visit) and the event time is the time of the last visit.

Participants failing to complete treatment and not assessable at the end of the follow-up period are considered to have an unfavorable outcome and the event time is the time of the last treatment dose received.

Participants receiving an extension of treatment, re-start of treatment, or change in treatment (see full definition B of unfavorable outcome) are considered to have an unfavorable outcome and the event time is the time of the treatment modification.</td></tr>
</table>

5. Pregnancy during treatment resulting in discontinuation of initial therapy Unevaluable outcome* (Composite strategy) **Intercurrent events that occur after adequate** completion of therapy:** 6. Death except from violent or accidental cause (e.g., road traffic accident) Unfavorable outcome (Composite strategy) 7. Violent or accidental death Unevaluable outcome* (Hypothetical strategy) 8. Extension of treatment beyond the nominal duration except to make up missed doses Unfavorable outcome (Composite strategy) 9. New TB diagnosis due to a new strain of *Mtb* Unevaluable outcome* (Hypothetical strategy) * See handling of missing data for imputation rules for unevaluable outcomes	Participants lost to follow-up after the treatment phase with their last available TB culture being negative are considered unevaluable and are censored at the time of the last visit. Participants who experience violent or accidental death are considered to have an unevaluable outcome and will be censored at the time of their last follow-up visit. Participants reinfected with a new strain of Mtb are considered to have an unevaluable outcome and will be censored at the time of their last follow-up visit. Participants who become pregnant during their assigned active treatment and who stop their assigned treatment are considered to have an unevaluable outcome and will be censored at the time of the last treatment dose received.
Population-level summary measure	Analysis approach
Difference in cumulative probability of having a favorable clinical/bacteriologic outcome at 65 weeks after TB therapy initiation .	Difference in cumulative proportion of participants at 65 week visit together with 90% and 95% two-sided confidence intervals. We will use the Kaplan-Meier estimator and Greenwood's estimate for the standard error.

** Adequate completion of therapy is determined by the following definitions:

<u>Definitions of Adequate Treatment Within 3-month Regimen (Arm 1 in the setting of this trial)</u>

- Taken a total of at least 56 doses of allocated intensive phase treatment within 70 days of starting treatment
- AND taken at least 28 doses of continuation phase treatment within 49 days (7 weeks) of completion of the intensive phase
- AND missed no more than 21 doses of medication overall.

Definitions of Adequate Treatment within 6-month Regimen (Arm 2 in the setting of this trial)

- Taken a total of at least 56 doses of allocated intensive phase treatment within 70 days of starting treatment
- AND taken at least 100 doses of continuation phase treatment within 154 days (22 weeks) of completion of the intensive phase
- AND missed no more than 42 doses of medication overall.

5.1.3 Secondary Objectives

5.1.3.1 Tolerability (Objective 2.3.2.2; Outcome Measure 3.2.2)

We will compare the proportion of participants who permanently and prematurely discontinue study treatment for any reason between arms in the start treatment/not late exclusion set. Permanent and premature discontinuation of study treatment is defined as not having completed an adequate dose of treatment as defined in Section 3.2.1. We will exclude participants who discontinued due to violent or accidental death, natural disaster, or administrative censoring (e.g. site closure), from the analysis. The difference in proportions will be estimated using binomial proportions, and we will provide exact 95% confidence intervals.

5.1.3.2 QT Prolongation (Objective 2.3.2.3; Outcome Measures 3.2.3.1, 3.2.3.2, 3.2.3.3)

We will compare the mean change in QTcF from screening to weeks 2, 8, and 13 (3.2.3.1) between Arm 1 and Arm 2 in the safety set using a GEE model with exchangeable correlation structure and time by treatment interaction terms (treating time as a categorical variable).

We will compare the change from baseline in QTcF over time between arms using a linear mixed effects model. Randomization arm and week (time) will be fixed effects and participant ID will be a random effect.

We will compare the odds of participants having maximum occurrence of absolute QTcF ≥ 480 ms and <500 ms, or ≥ 500 ms (3.2.3.2) between Arm 1 and Arm 2 in the safety set using a proportional odds model, if the proportional odds assumption is satisfied. We will assess the proportional odds assumption using the score test for the proportional odds assumption implemented in SAS PROC LOGISTIC. If the score test indicates a statistically significant result at the 0.05 level, we will also assess the proportional odds assumption graphically to confirm. If graphical evidence suggests the proportional odds model is valid, we will use it for analysis.

If the proportional odds assumption does not hold, we will instead estimate the difference in binomial proportions and 95% confidence intervals for the collapsed category of QTcF ≥ 480 ms (including QTcF ≥ 500 ms), and separately for the category QTcF ≥ 500 ms.

The analysis of outcome measure 3.2.3.3 will follow the same approach as that of 3.2.3.2.

5.1.3.3 Time to stable culture conversion in liquid media, and solid media at week 26 (Objective 2.3.2.4; Outcome Measure 3.2.4)

Time to stable culture conversion in liquid media will follow the same approach as described in Section 5.1.1, except we will censor participants at week 26 instead of week 12.

Time to stable culture conversion in solid media will be analyzed separately, and also follow the same approach as described in Section 5.1.1, except we will censor participants at week 26 instead of week 12.

5.1.3.4 Proportion with culture conversion at week 8 and 12 (Objective 2.3.2.5; Outcome Measure 3.2.5)

We will compare the proportion of participants with stable culture conversion by week 8 and week 12 between Arm 1 and Arm 2 in the efficacy set. We will analyze liquid and solid cultures separately. We will present the difference in proportions and exact 95% confidence intervals.

5.1.3.5 Proportion with one or more SAE (Outcome Measure 3.2.8)

We will estimate the proportion of participants with one or more SAEs of any grade between Arm 1 and Arm 2 in the safety set using the same approach as described in Section 5.1.1

As in Section 5.1.1, supplementary analyses will compare SAEs between arms up to week 13 and up to week 26.

5.1.3.6 Time to Positivity (Objective 2.3.2.6, Outcome Measure 3.2.6)

We will compare time (days) to positivity of TB cultures between Arm 1 and Arm 2 in the efficacy set separately at weeks 1, 2, 3, 4, 6, 8, 10, and 12 using Cox proportional hazards models or log-rank tests. We will present the hazard ratios and 95% confidence intervals for each week.

We will include side-by-side box plots to show the distribution of time to positivity at each visit in each of Arms 1 and 2. In exploratory analyses, we may consider comparing time (days) to positivity of TB cultures between Arm 1 and Arm 2 in the efficacy set using a random effects joint model for time-to-event data with repeated measures. We may also consider other models and mechanistic approaches.

5.1.3.7 Chest X-Ray Scores (Objective 2.3.2.7; Outcome Measure 3.2.7)

Each participant will have a CXR Score computed at screening and at EOT (week 13 for Arm 1; week 26 for Arm 2). We will compute the difference in scores from baseline to EOT between arms in the efficacy set using linear regression, with adjustment for stratification factors of HIV status and advanced disease status.

We will carry out two analyses for this outcome; (1) based on the site reading of CXR, and (2) based on the central reading of CXR. The central reading will take precedence when presenting results.

5.1.3.8 Proportion of participants who have a TB relapse (Objective 2.3.2.9; Outcome Measure 3.2.8)

We will estimate the proportion of participants in Arm 1 and Arm 2 with TB relapse using Kaplan-Meier estimates and 95% confidence intervals at 6 months (Arm 1), 9 months (Arms 1 and 2), and 12 months post-treatment (Arm 1 only) in the start treatment/not late exclusion set. We define the time of relapse as the time from end of treatment until the first sputum sample that is culture

positive in liquid or solid media for an *Mtb* strain that has matching genotype with the baseline isolate. A second positive sputum sample obtained at least 4 hours following the first sputum collection is required to confirm a relapse. If the second sputum sample is negative, this will not be counted as a relapse. If a participant is lost to follow-up without a second sputum sample confirmation of relapse (including contaminated or missing), it will be counted as a relapse.

For monitoring and interim reviews, we will estimate the proportion of participants with a confirmed relapse over time with 95% pointwise confidence bands. In addition, we will estimate the proportion of participants with a suspected TB recurrence or poor treatment response after successful culture conversion, even if relapse/recurrence has yet to be confirmed bacteriologically.

5.1.3.9 Proportion of Participants who have a TB recurrence (Objective 2.3.2.9; Outcome Measure 3.2.10)

The analysis for the proportion of participants with a TB recurrence will follow the same approach described in Section 5.1.3.8. We define recurrence in the same way as relapse, except it is not required that the TB strain has matching genotype with the baseline sample.

5.1.3.10 Plasma Pharmacokinetic Parameters for CFZ (Objectives 2.3.2.10 and 2.3.2.11; Outcome Measures 3.2.11)

Elin Svensson and team at Radboudumc, The Netherlands, will conduct this analysis.

The PK parameters of interest (Cmin, Cmax, Tmax, AUC0-24h) for CFZ in Arm 1 and Arm C of the alive/adequate treatment set will be estimated using non-compartmental methods applied to concentrations from intensive PK sampling visits. The AUC will be determined using the trapezoidal rule. Cmin will be the minimum observed concentration after the observed dose. Cmax will be the maximum observed concentration. Tmax is the time at which Cmax occurs.

Arm 1 versus Arm C

We will estimate the geometric mean ratio for each PK parameter (Cmin, Cmax, Tmax, AUC0-24h) together with the 90% confidence interval using available data in the alive/adequate treatment set.

This non-compartmental analysis will be in conjunction with non-linear mixed-effects modeling to estimate the primary PK parameters (e.g., apparent oral clearance (CL/F), volume of distribution, rate of absorption). The model-based analysis will use the intensive PK samples as well as the sparse samples collected throughout the study period and all protein concentration data. We will model the PK observations continuously over time, taking in account each participant's actual dosing history. We will conduct a covariate analysis to evaluate the potential impact of demographics and concomitant medications. We will compare the derived secondary metrics with the non-compartmental analysis results in a posterior predictive check.

5.1.3.11 CFZ-associated skin hyperpigmentation (Objective 2.3.2.12; Outcome Measures 3.2.12 and 3.2.13)

We will compute the total color difference scores using the CIELAB color space output values, (L, a, b), from the colorimeter device. Since each reading is done in triplicate, we will use the average scores from the three readings for L, A, and b for each participant. The analysis for each anatomical locations will be separate.

The CIE76 formula for total color difference, Delta E, is given by: $\Delta E = \sqrt{\Delta L^2 + \Delta a^2 + \Delta b^2}$

We will compare the mean change in total color difference (ΔE) from week 0 (entry) to each of weeks 8, 13, 26, 65 in Arm 1 vs Arm 2 at each of the following locations; (1) forehead, (2) left cheek, (3) right cheek, (4) chin in the mITT-B population. That is, for each anatomical location, we will compute the difference between ΔE at week 0 and week 8 for each of Arm 1 and Arm 2. We will compare the differences with a t-test.

We will also compare the mean change in total color difference (ΔE) from week 0 (entry) to each of weeks 8, 13, 26, 65 in Arm 1 vs Arm 2 using, for each participant in the safety set, the location with the maximum change. We will compare differences between arms with a t-test.

We will compare the 'mean change in coloration score' and 'mean distress related to skin coloration score' for Arm 1 vs Arm 2 at each of weeks 0, 8, 13, 26, and 65 in the safety set.

Using subjective assessments of clinical images, we will compare the proportion of participants with each degree of skin discoloration in Arm 1 vs Arm 2 in the safety set. We will provide the point estimates together with the Pearson Klopper exact 95% confidence intervals.

6 Primary Analysis Report Contents

All tables, listings, and figures provided in the final report will include totals and percentages by arm and overall unless otherwise specified. At a minimum, the final report will have the following contents.

6.1 Study Entry

- Accrual by site, country, and month
- Summary of late exclusions (number and reasons, by arm)
    - Participants whose screening, entry, and first post-entry visit sputum cultures all fail to grow *Mtb* complex,
      Or
    - Participants whose molecular or drug susceptibility test results demonstrate resistance to INH or RIF after enrollment

6.2 Baseline Characteristics

- Summary of age, sex, gender, country, Karnofsky Score (50-70, 80-100), BMI, HIV Status (stratification factor), advanced disease status determined by chest x-ray (stratification factor), Total CES Depression Scale Score, CD4 count among those HIV positive, viral load among those HIV positive
- Baseline TB diagnostic test results (AFB smear, drug susceptibility tests)
- Baseline lab results for AST, ALT, bilirubin, hemoglobin
- 2x2 table displaying concordance of site classification and central reader classification of advanced disease status by chest x-ray

6.3 Study Status

- Summary of off-study reasons
- Summary of participants last study visit week

6.4 Treatment Status

- Summary of number of participants who did not start study treatment
- Summary of extensions, changes, and restarts of study treatment
- Summary of reasons for permanently discontinuing study treatment
- Summary of number of participants who had an adequate dose of study treatment as defined in the protocol and Section 3.2.1 of this document.

6.5 Adverse Events

- Summary of post-entry reportable adverse events according to Section 7 of the protocol
- Summary of post-entry SAE
- Summary of QTcF at screening, weeks 2, 8, and 13
- Summary of difference in QTcF between screening, and weeks 2, 8, and 13
- Proportion with a maximum occurrence of QTcF ≥ 480 ms and < 500 ms, and ≥ 500 ms

- Proportion with a maximum change from screening of QTcF ≥30 ms and <60 ms, and ≥60 ms, at any time during study treatment
- Summary of Grade 3 or higher post-entry QT prolongation adverse events

6.6 Primary Outcome Measures

- Kaplan-Meier curve of time to stable culture conversion in liquid media, censored at 12 weeks (outcome measure 3.1.1)
- Hazard ratio and 90% two-sided confidence interval for time to stable culture conversion in liquid media (outcome measure 3.1.1)
- Proportions in each arm, and difference in proportions with 90% confidence interval of primary safety outcome at weeks 13, 26, and 65 (outcome measure 3.1.2)

6.7 Secondary Outcome Measures

- Proportions in each arm, and difference in proportions with corresponding confidence interval for outcome measures 3.2.1A and B, 3.2.2, 3.2.5, 3.2.6, 3.2.9, 3.2.10.
- Contrasts that estimate the difference between in mean change in QTcF scores between Arm 1 and Arm 2 from screening to weeks 2, 8, and 13 with corresponding 95% confidence intervals (outcome measure 3.2.3.1)
- Odds ratio and 95% confidence interval from proportional odds model for outcome measures 3.2.3.2 and 3.2.3.3. If proportional odds model does not hold, then difference in proportions for categories QTcF ≥ 480 ms and QTcF ≥ 500 ms between arms with corresponding 95% confidence intervals.
- Kaplan-Meier curves of time to culture conversion in liquid media, and solid media, censored at 26 weeks (outcome measure 3.2.4).
- Hazard ratio and 95% confidence intervals for time to culture conversion in liquid media, and solid media, censored at 65 weeks (outcome measure 3.2.4).
- Hazard ratio and 95% confidence intervals for time to positivity in liquid media at each time point. If proportional hazards does not hold, then we will report log-rank test. Side-by-side box plots of time to positivity (Days) at each time point (weeks 1, 2, 3, 4, 6, 8, 0, 12) (outcome measure 3.2.6)
- Estimates for changes in chest x-ray score in each arm from screening to EOT, and estimate of difference in change with 95% confidence interval (outcome measure 3.2.7)
- Contrasts that estimate the difference with corresponding 95% confidence interval between Arm 1 and Arm 2 for the change in total skin hyperpigmentation color difference from week 0 to each of weeks 8, 13, 26, and 65 at each of the following locations; (1) left cheek, (2) right cheek, (3) forehead, (4) chin, (5) using the location with the maximum change in total skin hyperpigmentation color difference. (outcome measure 3.2.12)
- Contrasts that estimate the difference in mean subjective ‘change in coloration score’ at each of weeks 0, 8, 13, 26, and 65 in Arm 1 vs Arm 2 with corresponding 95% confidence intervals (outcome measure 3.2.13)
  Contrasts that estimate the difference in mean subjective ‘distress to skin coloration’ score at each of weeks 0, 8, 13, 26, and 65 in Arm 1 vs Arm 2 with corresponding 95% confidence intervals (outcome measure 3.2.12)

7 Associated Documents

Attachment 1: Writing Team Roster

Protocol Chair	John Metcalfe, MD, PhD, MPH
Protocol Vice Chairs	Samuel Pierre, MD Kimberly Scarsi, PharmD, MS
DAIDS Clinical Representatives	Melanie Goth
Statisticians	Isabelle Weir, PhD Jorge Leon-Cruz, MS
Pharmacologists	Gary Maartens Elin Svenson
Dermatologist	Leo Shmuylovich

The reports will also be distributed to the TB TSG chair/vice chair and the ACTG network chair. The clinical trials specialist (CTS) and ACTGPublications@mednet.ucla.edu will be notified when the analysis report has been sent.

Attachment 2: Timetable for primary analysis and manuscript preparation

Event	Responsible party	Weeks from primary completion date (PCD)
Pre-closure conference call - Create specimen shipping and testing plan for laboratory data - Check about MTAs - Initiate DTAs	CTS Protocol team NCC LDM	PCD - 26 weeks
Primary completion date (PCD)		PCD
Clinical data entry termination	Sites	PCD + 1 week
Final specimen shipping request of samples to testing laboratories	LDM	PCD + 2 weeks
Initial database clean-up complete, including - DAERS reconciliation complete - TSDV complete	PDM and LDM	PCD + 12 weeks
Laboratory data submitted to Frontier Science	Assay laboratory	PCD + 12 weeks

Clinical database closure/freeze complete/eCRF sign-off by site investigators	PDM and Sites	PCD + 15 weeks
SDTM ARMCD populated	SDTM Specialist	PCD + 16 weeks
Processing & QC of laboratory data complete	LDM	PCD + 16 weeks
Complete SDTM on production server	SDTM Specialist	PCD + 18 weeks
Clinical database lock and primary laboratory database lock	Chief Data Manager and LDM Leadership	PCD + 21 weeks
Final SDTM on production server	SDTM Specialist	PCD + 22 weeks
Primary analysis report to protocol Chairs/Writing Team	Protocol statisticians	PCD + 26 weeks