

Otsuka Pharmaceutical Development & Commercialization, Inc

Investigational New Drug quabodepistat (OPC-167832)

Protocol No. 323-201-00006

IND No. 129303

A Multicenter, Phase 2b/c, Open-label, Randomized, Dose-finding Trial to Evaluate the Safety and Efficacy of a 4-month Regimen of OPC-167832 in Combination with Delamanid and Bedaquiline in Participants with Drug-susceptible Pulmonary Tuberculosis in Comparison with Standard Treatment

Statistical Analysis Plan

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Table of Contents

Title Page.....	1
Table of Contents	2
List of Tables.....	6
List of Figures	7
List of Appendices	8
List of Abbreviations and Definition of Terms.....	9
1 Introduction	11
2 Trial Objectives	11
2.1 Primary Objective	11
2.2 Secondary Objectives	11
2.3 Exploratory Objective - Biomarkers	11
2.4 Exploratory Objective - Efficacy	12
3 Trial Design.....	12
3.1 Type/Design of Trial	12
3.2 Trial Treatments	12
3.2.1 Treatment Descriptions.....	13
3.3 Trial Population.....	14
3.4 Trial Visit Window.....	14
4 Sample Size	14
5 Statistical Analysis Datasets	15
5.1 All Participants Set.....	15
5.2 Randomized Analysis Set.....	15
5.3 Modified Intent-to-Treat Analysis Set	15
5.4 Safety Analysis Set.....	16
5.5 Completers or Partial Completers Analysis Set	16
5.5.1 Completers or Potential Completers Analysis Set (CPC).....	17
5.5.2 Completers or Potential Completers_8 Analysis Set (CPC_8).....	17
5.6 Per Protocol Analysis Set.....	17

CCI

Statistical Analysis Plan

Protocol 323-201-00006

6	Handling of Missing Data	18
6.1	Missing Data for Sputum Culture Conversion	18
7	General Considerations for Statistical Analyses	19
7.1	Continuous Variables	19
7.2	Categorical Variables	19
7.3	Stratification Factors/Stratum	19
8	Primary and Secondary Outcome Variables	20
8.1	Primary Outcome Variables	20
8.1.1	Primary Efficacy Variable	20
8.1.2	Primary Safety Variables	22
8.1.2.1	Adverse Events	23
8.1.2.2	Clinical Laboratory Data	24
8.1.2.3	Vital Signs	24
8.1.2.4	Electrocardiogram Data	24
8.1.2.5	Physical Examination Data	25
8.1.2.6	Rate of All-Cause Treatment Discontinuation	25
8.2	Secondary Outcome Variables	25
8.2.1	Secondary Efficacy Variables	25
8.2.1.1	Sputum Culture Conversion in MGIT by 8 Weeks	26
8.2.1.2	Time to Positivity/Time to Detection of MGIT Cultures	26
8.2.1.3	Sputum Lipoarabinomannan Concentration	27
8.2.1.4	Drug Resistance	28
8.2.1.5	Time to Sputum Culture Conversion (SCC)	28
8.3	Exploratory Outcome Variables	29
8.3.1	Exploratory Efficacy Variables	29
8.3.1.1	Favorable Outcome	29
8.3.1.2	Relapse	30
8.3.2	Exploratory Biomarker Variables	30
9	Disposition and Demographic Analysis	31
9.1	Participant Disposition	31
9.2	Reasons for Discontinuation	31
9.3	Demographic and Baseline Characteristics	32

Statistical Analysis Plan

Protocol 323-201-00006

9.4	Medical History	32
9.5	Treatment Exposure and Compliance	32
9.6	Prior and Concomitant Medication	33
9.7	Rescue Treatment/Medications	34
9.8	Protocol Deviations	34
10	Efficacy Analyses.....	35
10.1	Primary Efficacy Analyses	35
10.2	Secondary Efficacy Analyses	36
10.2.1	Sputum Culture Conversion in MGIT by 8 Weeks	36
10.2.2	Time to Positivity/Time to Detection of MGIT Cultures	36
10.2.3	Sputum Lipoarabinomannan.....	36
10.2.4	Drug Resistance	36
10.2.5	Time to Sputum Conversion.....	37
10.3	Exploratory Efficacy Analyses.....	37
10.4	Exploratory Biomarker Analyses	38
10.5	Sensitivity Analyses	38
10.6	Subgroup Analyses.....	39
11	Safety Analyses	39
11.1	Extent of Exposure	39
11.2	Adverse Events.....	39
11.3	Clinical Laboratory Data	40
11.4	Vital Sign Data	40
11.5	Electrocardiogram Data.....	41
11.6	Physical Examination Data	41
11.7	Clinical Signs and Symptoms of Tuberculosis	41
11.8	Other Safety Data	42
CCI		
13	Pharmacogenomic Analyses	42
14	Bioavailability Analyses.....	42
CCI		
16	Data Monitoring Committee Analyses	43

Statistical Analysis Plan

Protocol 323-201-00006

17	Changes in Planned Analysis	43
18	Document History	44
19	References	47
20	Appendices	48

Statistical Analysis Plan

Protocol 323-201-00006

List of Tables

Table 3.2.1-1	Rifinah Dosing Table.....	14
Table 8.1.1-1	Baseline Visit and Baseline Visit Result Determination	20
Table 8.1.1-2	Interpretation of (Regular) MGIT Sputum Culture Results	22

Statistical Analysis Plan

Protocol 323-201-00006

List of Figures

Figure 3-1	Trial Design Schematic.....	12
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Statistical Analysis Plan

Protocol 323-201-00006

List of Appendices

Appendix 1	Definition of Grades in Serum Chemistry, Hematology and Urinalysis Lab Test Results in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events49
Appendix 2	Definition of Grades for Vital Signs in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events53
Appendix 3	Sponsor Provided Criteria for Identifying Vital Sign Measurements of Potential Clinical Relevance54
Appendix 4	Sponsor Provided Criteria for Identifying ECG Measurements of Potential Clinical Relevance55
Appendix 5	Completer Category Information.....58
Appendix 6	Missing Data for Adverse Events/Concomitant Medications60
Appendix 7	SAS Code.....62
Appendix 8	Determination of 6-month Post End-of-Treatment Favorable/Unfavorable/Not Assessable Outcome63

Statistical Analysis Plan

Protocol 323-201-00006

List of Abbreviations and Definition of Terms

<u>Abbreviation</u>	<u>Definition</u>
ACD	actual cumulative dose
ADI	actual dose intensity
AE	adverse event
BDQ	Bedaquiline
BMI	body mass index
CI	confidence interval
CPC	completers or potential treatment completers
CRF	case report form
CSR	clinical study report
CT	computerized axial topography
DAIDS	Division of AIDS
DBO	delamanid, bedaquiline, OPC-167832 (quabodepistat)
DCO	data cutoff date
DLM	Delamanid
DMC	data monitoring committee
DOT	directly observed therapy
DS-TB	drug-susceptible pulmonary tuberculosis
ECG	Electrocardiogram
FO	favorable outcome
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
CCI	
ICH	International Council for Harmonisation
IMP	investigational medicinal product (includes any delamanid, bedaquiline and quabodepistat [OPC-167832] and any rifampin, isoniazid, ethambutol, pyrazinamide) provided to a participant as study medication
IRT	interactive response technology
KM	Kaplan-Meier
LAM	Lipoarabinomannan
LTFU	lost to follow-up
MGIT	Mycobacteria Growth Indicator Tube®
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
MTB/MTb	Mycobacterium tuberculosis
PCR	potential completers
PCS	potentially clinically relevant
PDI	planned dose intensity
PET	positron emission tomography
CCI	
PP	per protocol
QD	Daily
RDI	relative dose intensity
RHEZ	rifampin, isoniazid, ethambutol, pyrazinamide
RS	rRNA synthesis ratio
SAE	serious adverse event
SAP	statistical analysis plan
SCC	sputum culture conversion
SD	standard deviation

Statistical Analysis Plan

Protocol 323-201-00006

<u>Abbreviation</u>	<u>Definition</u>
SLC	sputum lipoarabinomannan conversion
TB	Tuberculosis
TIW	three times weekly
TEAE	treatment-emergent adverse event
TTD	time to detection
TTP	time to positivity
w	With
wo	Without
wwom	with and without mitigation

1 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of safety and efficacy data of Trial 323-201-00006. This SAP is based on Amendment 2 of the Protocol dated 08 Oct 2021 CCI [REDACTED]

Trial 323-201-00006 is a phase 2 trial for quabodepistat (OPC-167832) that is being developed for the treatment of pulmonary tuberculosis, an infection caused by *Mycobacterium tuberculosis*. The statistical analyses and summary tabulations described in this SAP will provide the basis for all the analyses conducted during the course of the trial and also for the final analysis outputs with the results and appendices of the clinical study report (CSR) for this study.

2 Trial Objectives

2.1 Primary Objective

The primary objective of this trial is to assess the safety and efficacy of quabodepistat (OPC-167832) combined with delamanid (DLM) and bedaquiline (BDQ) in participants with drug-susceptible pulmonary tuberculosis (DS-TB) administered for 4 months compared to standard of care administered for 6 months (RHEZ).

2.2 Secondary Objectives

- To evaluate the efficacy using sputum Mycobacteria Growth Indicator Tube® (MGIT) culture and lipoarabinomannan (LAM) concentration for quabodepistat (OPC-167832) combined with DLM and BDQ administered for 4 months as compared to RHEZ.
- To evaluate the development of resistance to anti-tuberculosis (TB) drugs in all treatment arms.
- To inform dose selection of quabodepistat (OPC-167832) combined with DLM and BDQ.

2.3 Exploratory Objective - Biomarkers

- To evaluate various novel biomarkers for association with microbiological and clinical response.

2.4 Exploratory Objective - Efficacy

- To evaluate the efficacy of experimental arms in comparison to RHEZ through the end of the post-treatment follow-up period.

3 Trial Design

3.1 Type/Design of Trial

Trial 323-201-00006 is a multicenter, phase 2b/c, open-label, randomized, dose-finding trial in participants with DS-TB. The microbiology laboratory will be blinded to treatment assignments. Following a screening period of up to 14 days, eligible participants will be randomized on Day -1 or predose Day 1 in a ratio of 1:2:2:1 to one of the four treatment arms (Figure 3-1). Randomization will be stratified by human immunodeficiency virus (HIV) status (yes or no) and presence of bilateral cavitation on screening chest x-ray (yes or no). At the end of the treatment period, participants will be followed until 12 months post randomization.

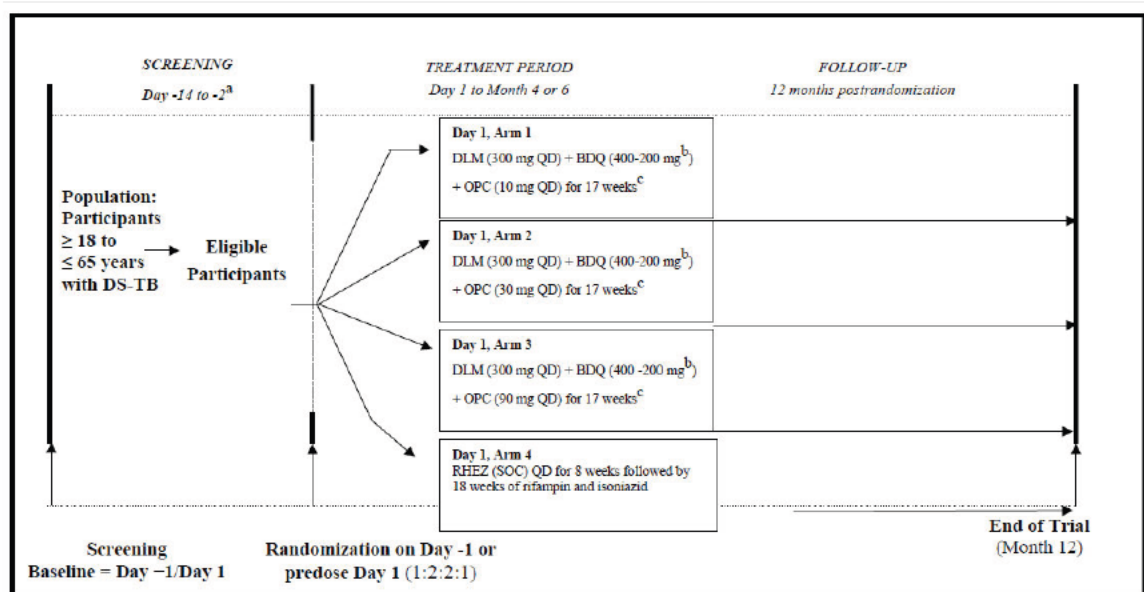


Figure 3-1 Trial Design Schematic

3.2 Trial Treatments

Treatment Arms 1, 2, and 3:

Investigational medicinal product (IMP) (i.e. quabodepistat [OPC-167832], DLM, or BDQ) in Arms 1-3 must be administered after the completion of a meal.

Statistical Analysis Plan

Protocol 323-201-00006

Bedaquiline should be administered as follows: 400 mg daily (QD) for the first 2 weeks of treatment and 200 mg three times weekly (TIW) thereafter with at least 48 hours between doses for the remainder of the trial (i.e., a total of 17 weeks [Arm 1 or Arm 2 or Arm 3] of treatment).

IMP will be administered using the locally accepted adherence monitoring techniques which could include directly observed therapy (DOT), Wisepill, video DOTs, or other adherence monitoring techniques. In addition, all doses of IMP given during trial visits will be observed via the hand-and-mouth procedure. IMP will be administered with approximately 240 mL of still (noncarbonated) water.

Treatment Arm 4:

Participants randomized to treatment Arm 4 will receive RHEZ orally QD for 8 weeks followed by 18 weeks of rifampin and isoniazid per the local standard of care. RHEZ will be administered using the locally accepted adherence monitoring techniques which could include DOT, Wisepill, video DOTs, or other adherence monitoring techniques. In addition, all doses of RHEZ given during trial visits will be observed via the hand-and-mouth procedure. RHEZ will be administered with approximately 240 mL of still (noncarbonated) water. The RHEZ will be taken 1 hour prior to or 2 hours after a meal.

3.2.1 Treatment Descriptions

Arm 1: DLM (300 mg once daily [QD]) + BDQ (400 mg QD × 2 weeks, then 200 mg thrice - weekly [TIW]) + OPC-167832 (10 mg QD) for 17 weeks

Arm 2: DLM (300 mg QD) + BDQ (400 mg QD × 2 weeks, then 200 mg TIW) + OPC-167832 (30 mg QD) for 17 weeks

Arm 3: DLM (300 mg QD) + BDQ (400 mg QD × 2 weeks, then 200 mg TIW) + OPC-167832 (90 mg QD) for 17 weeks

Arm 4: RHEZ for 8 weeks followed by 18 weeks of rifampin and isoniazid (for a total of 26 weeks)

Dosing of Rifafour® (RHEZ) will be determined by the participant's weight assessed at each visit where vital signs and weight are assessed.

Weight will be rounded to the next whole number (e.g., 1.1-1.4 = 1; 1.5-1.9 = 2).

Dosing will be based on the participant's weight:

- Participants weighing 30 to 37 kg will receive 2 tablets per day.
- Participants weighing 38 to 54 kg will receive 3 tablets per day.
- Participants weighing 55 to 70 kg will receive 4 tablets per day.

- Participants weighing > 70 kg will receive 5 tablets per day.

Dispense sufficient RHEZ tablets into a clearly labelled container for the subject to complete treatment for the next week and allow for the window period. The label should contain name RHEZ, protocol number, the site name and address, instructions for use, route of administration, and appropriate precautionary statements.

Dosing of Rifinah will be determined by the participant's weight assessed at each visit where vital signs and weight are assessed (see [Table 3.2.1-1](#)). Weight will be rounded to the next whole number (e.g., 1.1-1.4 = 1; 1.5-1.9 = 2).

Table 3.2.1-1 Rifinah Dosing Table		
Participant weight	Number of tablets daily	
	RIFINAH 150/75	RIFINAH 300FC
30 – 37 kg	2	-
38 – 54 kg	3	-
≥55 kg	-	2

3.3 Trial Population

The trial population will consist of participants who are ≥ 18 years to ≤ 65 years at screening with body weight of ≥ 35.0 kg and who have newly diagnosed pulmonary DS-TB. Approximately 120 participants (including no more than 15% with HIV-coinfection) will be enrolled at approximately 8 sites in South Africa.

3.4 Trial Visit Window

During treatment for Week 1 through Week 26 (Visits 3 through 20), the visit can be target day ± 2 days. During the follow-up period of Week 28 through Week 52 (Visits 21 through 27), the visit can be target day ± 7 days.

4 Sample Size

It is planned to enroll enough participants so that there will be 20 participants in the DLM + BDQ + 10 mg OPC-167832 arm, 40 participants each in the DLM + BDQ + 30 mg OPC-167832, and DLM + BDQ + 90 mg OPC-167832 arms, and 20 participants in the RHEZ group. This is a pilot trial and exploratory in nature. Thus, 80% CIs between proportion differences will be calculated to compare with noninferiority margin.

Assuming that the sputum culture conversion (SCC) rate at the end-of-treatment for the primary endpoint is 93% for the RHEZ group, and assuming the SCC rate of the quabodepistat (OPC-167832) arms is identical to the RHEZ group, with a noninferiority margin of 12%, a sample size of 120 participants (100 for pooled the DLM + BDQ + OPC-167832 arms and 20 for RHEZ) will have about 84% power to reject the null

Statistical Analysis Plan

Protocol 323-201-00006

hypothesis with a one-sided alpha level of 0.1, i.e., the lower limit of the two-sided 80% CI of the difference in proportions of sputum culture conversion between the pooled investigational arms and RHEZ is larger than -0.12 . The Miettinen and Nurminen method to construct 80% CI was used in the sample size calculation. Assuming 11% randomized participants will not demonstrate at least 1 positive culture result by Week 1 and susceptibility to rifampin and isoniazid, approximately 135 participants will be randomized in 1:2:2:1 ratio to obtain 120 participants in the modified intent-to-treat (mITT) analysis set.

5 Statistical Analysis Datasets

5.1 All Participants Set

The All Participants set will include all enrolled participants, that is, participants who have given signed informed consent. Screen failures includes participants who signed informed consent but were not randomized into the trial either because they did not meet the eligibility criteria or for any other reason (such as the study recruitment was complete). This analysis set will be used for inclusion/exclusion criteria, and screen failures.

5.2 Randomized Analysis Set

This analysis set comprises all enrolled participants who are randomized into the trial. Participants are considered randomized when they are assigned a randomization number and are assigned to a treatment arm.

This will be used for protocol deviations, participant disposition and medical history.

5.3 Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set includes randomized participants that have met all the below:

- have taken at least 1 dose of IMP or RHEZ,
- have at least 1 postbaseline culture result,
- demonstrate positive culture results by Week 1,
- demonstrate susceptibility to rifampin and isoniazid (from the screening specimen).

In the case where Week 1 is the baseline for MGIT cultures, then a post baseline culture will be defined as Week 2 or later. The mITT analysis set will be used for efficacy analyses. Tables on the mITT analysis set are presented according to the arm to which a participant was randomized (the planned treatment), regardless of actual treatment received.

5.4 Safety Analysis Set

The safety analysis set includes all randomized participants who take any dose of IMP (Arms 1 – 4). Participants will only be excluded from this population if the participant did not receive any IMP. Safety analysis will be presented by actual treatment received.

Safety analysis will be conducted based on the safety analysis set.

5.5 Completers or Partial Completers Analysis Set

Definition of Completed Participants

The treatment period is defined as the time period during which participants are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the participant actually took all doses of the IMP. For the purpose of this trial, treatment completers will be randomized participants who take IMP through either Week 17 (for Arm 1, Arm 2, and Arm 3) or Week 26 (for Arm 4) and complete at least some of the end-of-treatment assessments. Trial completers will be randomized participants who remain on the study till the 12 months post randomization visit.

Completer categories are as follows:

- Treatment completer and trial completer
- Treatment non-completer and trial completer
- Treatment completer, trial non completer
- Treatment non-completer and trial non-completer.

Details are as in [Appendix 5 Completer Category Information](#)

Note that “treatment completer” and “trial completer” are definitions requiring the participant to have been on the study for the entire treatment duration and trial duration respectively. Participants who discontinue or die would not be entered as “completed” in the CRF disposition page. The participant disposition table will be based on the disposition entered for the participant in the CRF, and the treatment or trial completer status as assessed by the criteria listed in [Appendix 5 Completer Category Information](#)

5.5.1 Completers or Potential Completers Analysis Set (CPC)

This analysis set will be used for analyses prior to final database lock, where a data cutoff has to be applied. Participants with ongoing treatment at data cutoff are excluded from the Completers or Potential Completers (CPC) analysis set.

The CPC analysis set comprises of mITT participants who are also treatment completers or potential treatment completers. Treatment completers are participants who have been exposed to IMP and do not discontinue treatment during the treatment period (17 weeks for quabodepistat (OPC-167832) arms/26 weeks for RHEZ arm). Potential completers are participants who could have completed treatment (by data cutoff as applicable for Data Monitoring Committee [DMC] CCI [REDACTED] had they not discontinued treatment, died or become lost-to-follow-up prior to completing treatment.

Note that for data cutoffs that are post end-of- treatment, (or potential end-of-treatment for discontinuing participants) for all participants, reports on the CPC analysis set will not be generated.

5.5.2 Completers or Potential Completers_8 Analysis Set (CPC_8)

This analysis set will be used for the “8 weeks” analyses prior to final database lock, where a data cutoff has to be applied.

The CPC_8 analysis set comprises of mITT participants who are also 8-week treatment completers or potential 8-week treatment completers. 8-week treatment completers are participants who have been exposed to IMP and do not discontinue treatment in the first 8 weeks of the treatment period. Potential 8-week completers are participants who could have completed 8 weeks of treatment by data cutoff, had they not discontinued treatment, died or become lost-to-follow-up prior to completing the 8-weeks on treatment. Only participants who have not completed 8-weeks of treatment by data cutoff, that is, are ongoing participants at data cutoff, are excluded from the CPC_8 analysis set.

Note that for data cutoffs that are post 8-weeks treatment (or potential 8-week treatment completion) for all participants, reports on the CPC_8 analysis set will not be generated.

5.6 Per Protocol Analysis Set

The per protocol (PP) analysis set comprises of participants from mITT analysis set excluding those satisfying any of the criteria mentioned below:

- patients who do not meet eligibility criteria.
- participants who are found to have less than or equal to 80% adherence of any of the IMP or discontinued IMP for a reason other than death, TB or TB-related

Statistical Analysis Plan

Protocol 323-201-00006

disease, or are who are determined to have major treatment adherence protocol violations.

- patients with major protocol deviations that impact primary efficacy analyses.

The final decision on the PP analysis set will be taken by the medical lead, clinical operations lead, and statistician. Participants will be analyzed according to actual treatment received.

The PP analysis set will be used for sensitivity analyses of select efficacy data.

Reasons for excluding a participant from the PP analysis set will be summarized and listed.

In addition to select efficacy analyses, analyses such as disposition, demographics and baseline characteristics, and exposure tables will be generated for comparability of treatment arms for the PP analysis set.

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6 Handling of Missing Data

Unless specified in this SAP, all data will be evaluated as observed, and no imputation method for missing values will be used. If values are imputed for missing data, these will be flagged in listings. Situations in which data may be imputed is specified in the handling of missing data [Section 6.1](#) and efficacy analysis [Section 10](#).

Missing dates for dates of Concomitant Medications and Adverse Events will be imputed as described in

[Appendix 6 Missing Data for Adverse Events/Concomitant Medications](#)

6.1 Missing Data for Sputum Culture Conversion

All randomized participants will be sputum culture positive at baseline.

Modified intent-to-treat (mITT) participants who discontinue or die prior to treatment completion, will be assessed based on the MGIT sputum culture assessments till the date of discontinuation or death. mITT participants who remain on the trial till the end-of-treatment but have two or more missing consecutive sputum culture assessments at the

Statistical Analysis Plan

Protocol 323-201-00006

end of treatment, will be considered as not having achieved SCC (SCC = “No”) for the end-of-treatment endpoint.

If there are missing cultures between 2 negative sputum cultures, the definition of conversion is still met, and the participant will be counted as having SCC.

Contaminated sputum cultures and Mycobacterium other than Tuberculosis will be defined as missing culture assessments for the primary analyses.

7 General Considerations for Statistical Analyses

General considerations for descriptive statistics and presentation for continuous and categorical data are given below.

All analyses will be presented by the 4 treatment arms and overall. In addition, for a few select efficacy tables, summaries for the pooled quabodepistat (OPC-167832) arms may also be included.

7.1 Continuous Variables

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation, median, minimum, and maximum.

Means, medians, and CIs will be reported to one decimal place more than the data reported on the CRF or by the vendor. Standard deviation (SD) will be reported to two decimal places more than the data reported on the CRF or by the vendor. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the vendor. P-values will be reported to 4 decimal places. Heart rates and ECG will be presented without any decimals for all summary statistics. The average of triplicate ECGs will be presented rounded to the nearest integer.

7.2 Categorical Variables

For categorical variables, the counts and proportions (as percentages) of each category for each parameter will be calculated. Percentages will be presented with one decimal place. The denominator for all percentages, unless otherwise specified, will be the number of participants in the specified treatment arm, overall group or cohort (e.g., subgroup) in the specified analysis population.

7.3 Stratification Factors/Stratum

Randomization will be stratified by HIV status (yes or no) and presence of bilateral cavitation on screening chest x-ray (yes or no). If there is a stratum of very small size, strata may be collapsed. For instance, if there are less than 5 HIV participants randomized

Statistical Analysis Plan

Protocol 323-201-00006

into the study in the OPC-167832 arms combined, or in the RHEZ arm, then the analysis will not use this stratification variable to adjust the estimates, similarly for bilateral cavitation status.

Descriptive analyses may be presented by stratification factors wherever needed. When statistical models are applied, the analysis may be done with and without adjustment for stratification factors (or collapsed stratification factors, as the case may be). Analytical methods will be specified in presentations.

Strata identification will be based on CRF data.

8 Primary and Secondary Outcome Variables

8.1 Primary Outcome Variables

8.1.1 Primary Efficacy Variable

Efficacy will be assessed by the proportion of participants achieving SCC in Mycobacteria Growth Indicator Tube® (MGIT) by the end of the treatment period. The treatment period is 17 weeks for arms with quabodepistat (OPC-167832) and 26 weeks for the RHEZ arm. Participants in the OPC-167832 arms will be pooled and compared to those in the RHEZ arm. The baseline for sputum culture will be Day 1 if the Day 1 result is positive. If the Day 1 result is negative, then the Day –1 result will be used as baseline. If the Day –1 result is also negative then the Week 1 result will be used as baseline, which in this case, must be positive. The treatment period will be from baseline to the end of the treatment period (last dose date of IMP). Below is an example decision table to determine the baseline visit result.

Note that SCC is a binary endpoint.

Table 8.1.1-1 Baseline Visit and Baseline Visit Result Determination								
Visit	Results							
Day –1	Positive	Negative	Negative	Negative	Positive	Positive	Positive	Negative
Day 1	Negative	Positive	Negative	Positive	Negative	Positive	Positive	Negative
Week 1	Negative	Negative	Positive	Positive	Positive	Negative	Positive	Negative
Baseline Visit	Day –1	Day 1	Week 1	Day 1	Day –1	Day 1	Day 1	-
Baseline Visit Result	Positive	Positive	Positive	Positive	Positive	Positive	Positive	-

A participant with negative sputum culture results at all three timepoints (last column) will be deemed ineligible for the mITT analysis set used for the efficacy analysis.

Statistical Analysis Plan

Protocol 323-201-00006

As per protocol, up to 3 MGIT samples will be collected at each visit except on Day –1 and Day 1, when only two samples will be collected. Only two of the samples are used for MGIT analysis. The third sample is used for rRNA synthesis ratio (RSA). MGIT culture will be performed on sputum specimen without (wo) any mitigation method applied and also with (w) a mitigation method applied.

For primary analysis of SCC, time to detection (TTD) or Kaplan-Meier (KM) plots, only the two MGIT samples without mitigation will be considered, i.e., (regular) MGIT. A sensitivity analyses will be performed using all 4 MGIT samples with and without mitigation (wwom).

For the primary analyses the following rules will be used with regular MGIT samples, at each visit:

- Both samples have a result, and this result is not “contaminated” or “other” as recorded on the CRF:
 - both results are positive for *Mycobacterium tuberculosis* (MTB) complex, the SCC result will be positive.
 - both results are negative for MTB complex, the SCC result will be negative.
 - one result for MTB complex is positive and one is negative, the result will be positive.
- If both samples are missing or both are contaminated/other, the result will be missing.
- If one sample is “contaminated”/“other”/or is missing, and the other is positive, the result will be positive.
- If one sample is “contaminated”/“other”/or is missing, and the other is negative, the result will be negative.

See [Table 8.1.1-2](#) for interpretation of each sample.

Sensitivity analyses interpreting CRF results differently from what is presented in [Table 8.1.1-2](#), may be considered to assess worst case and best-case scenarios. Details of these analyses will be specified in programming specifications.

Definition of sputum culture conversion (SCC):

Statistical Analysis Plan

Protocol 323-201-00006

SCC occurs when a participant has the first of 2 consecutive visits of at least 7 days apart with sputum culture assessment interpretations as “negative”, without a positive sputum culture result in between and no subsequent positive sputum culture during the treatment period (either end-of-treatment or 8 weeks). The date of collection for the first sample out of these 2 consecutive samples that is negative is considered as the date of conversion. If there are missing or contaminated/other culture results between 2 negative sputum culture assessments, the definition of conversion is still met.

The numerator of the proportion of participants will be the number of mITT participants who have achieved SCC by the end of the treatment period within the quabodepistat (OPC-167832) arms or the RHEZ arm. The denominator will be the total number of mITT participants within the arms being compared. See [Section 6.1](#) for handling of missing data for SCC.

The MGIT cultures will be interpreted as follows:

Table 8.1.1-2 Interpretation of (Regular) MGIT Sputum Culture Results	
CRF Results	Interpretation
Positive for MTB Complex	Positive
Positive for MTB Complex with Contamination	Positive
Mycobacteria other than MTB	Negative
Negative for MTB Complex	Negative
Contaminated	Missing
Missing results	Missing
Other	Missing

8.1.2 Primary Safety Variables

Safety and tolerability will be assessed based on the following data:

- Incidence of adverse events (AE), serious adverse events (SAE), treatment-emergent adverse events (TEAE), serious treatment emergent adverse events, AEs leading to discontinuation and TEAEs leading to discontinuation, Related TEAEs, TEAEs leading to Death, TEAEs by Severity (described in [Section 8.1.2.1](#)).
- The incidence of Potentially Clinically Relevant abnormal findings in clinical laboratory tests (serum chemistry, hematology, urinalysis, and coagulation) (described in [Section 8.1.2.2](#)).
- Potentially Clinically Relevant findings and abnormalities in vital signs (described in [Section 8.1.2.3](#)).
- Incidence of Potentially Clinically Relevant Abnormalities in Electrocardiogram Parameters (described in [Section 8.1.2.4](#)).
- Electrocardiograms (ECGs) (described in [Section 8.1.2.4](#)).
- Physical examinations (described in [Section 8.1.2.5](#)).

Statistical Analysis Plan

Protocol 323-201-00006

- Incidence of TEAEs with a DAIDS Toxicity grade ≥ 3 (described in [Section 8.1.2.1](#)).
- Rate of all-cause treatment discontinuation (described in [Section 8.1.2.6](#)).

8.1.2.1 Adverse Events

AEs will be collected from the signing of informed consent to the end of trial visit after the follow-up period or till complete withdrawal of consent. Serious adverse events are followed until resolution, stabilization, lost to FU or death.

All AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA; Version 25.0 or newest available) system organ class and preferred term.

Treatment-emergent AEs (TEAE) are defined as AEs with an onset date on or after the start of treatment with the IMP. In more detail, TEAEs are all AEs which started after the start of IMP treatment; or if the event was continuous from baseline and was worsening, serious, IMP related, or resulted in death, discontinuation, interruption, or reduction of IMP.

A serious adverse event is defined as an AE that leads to death, is life threatening, requires or prolongs hospitalization, significant disability, congenital anomaly or birth defect, and other medically important serious advent.

Non-serious AEs are AEs not classified as “Serious”.

Causality to IMP is classified as: related; not related.

AEs are graded in two ways. First, on a severity 3-point scale as follows: Mild; Moderate; Severe. In addition, all AEs will be graded on a 5-point scale according to DAIDS Table for Grading the Severity of Adult and Pediatric AEs¹ as follows: Grade 1 – Mild; Grade 2 – Moderate; Grade 3 – Severe; Grade 4 – Life Threatening; Grade 5 – Death.

Outcome of AE is classified as: Not recovered/not resolved; Recovered/resolved; Recovering/resolving; Recovered/resolved with sequelae; Fatal; Unknown.

Action taken with Study Treatment is classified as: Dose not changed; Dose reduced; Drug interrupted; Drug withdrawn; Not applicable.

Reporting of Adverse Events is described in [Section 11.2](#).

8.1.2.2 Clinical Laboratory Data

Clinical hematology, chemistry, coagulation and urinalysis are tested at: Screening, Day –1, Week 2, Week 4, Week 6, Week 8, Week 13, Week 17, Week 21, Week 26, Week 52, and end of study.

For clinical laboratory tests data, baseline is defined as the last non-missing value obtained at a scheduled visit on or before Day –1. If the Day –1 measurement is missing, the baseline value will be the non-missing measurement from the screening visit (the previous scheduled visit). Unscheduled visits will only be presented in the listings.

Reporting of Clinical Laboratory Data is described in [Section 11.3](#).

8.1.2.3 Vital Signs

Vital signs are taken at: Screening, Day –1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 13, Week 15, Week 17, Week 21, Week 26, Week 28, Week 30, Week 34, Week 39, Week 43, Week 47, Week 52, and end of study.

Vital signs include systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (rpm), body temperature (C), height (cm) (only at screening), weight, and body mass index (BMI). Baseline is defined as the last non-missing value obtained at a scheduled visit on or before Day –1. If the Day –1 measurement is missing, the baseline value will be the non-missing measurement from the screening visit (the previous scheduled visit).

Vital signs will be obtained prior to CCI and ECGs. At screening, blood pressure and heart rate will be taken with the participant in the supine (performed first) and sitting position after remaining for ≥ 3 minutes in each position and temperature and respiratory rate will be taken with the participant in the supine position. At all other time points, vital signs will be obtained after the participant has been at rest in the supine position for at least 1 minute. Unscheduled visits will only be presented in the listings.

Reporting of Vital Signs is described in [Section 11.4](#).

8.1.2.4 Electrocardiogram Data

ECG measurements are taken at: Screening, Day –1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 13, Week 15, Week 17, Week 21, Week 26, Week 30, Week 34, Week 39, Week 43, Week 47, Week 52, and end of study.

One standard 12-lead ECG will be performed during screening, plus 3 ECGs at baseline (Day –1) spaced 5 to 10 minutes apart, and 3 ECGs at all subsequent visits during the treatment and follow-up periods. Baseline is defined as the last non-missing value

Statistical Analysis Plan

Protocol 323-201-00006

obtained at a scheduled visit on or before Day –1. Findings detected by the investigator will also be categorized as baseline using the last non-missing value obtained at a scheduled visit on or before Day –1. Where multiple ECGs are required in a visit, the participant should be recumbent for 10 minutes prior, if possible, and ECG should be collected 5 to 10 minutes apart after the dose of IMP CCI. If additional ECGs were obtained at a time point at a site, all of the ECGs obtained at the time point will be averaged to provide for a more accurate point estimate of ECG intervals at that time point. If there are multiple ECG interpretation records, if one is Abnormal then the overall classification is Abnormal. The number of records with abnormal interpretation will be included in parentheses (x/n) where x is the number of “abnormal” interpretation records and n is the total number of records. This will be included in listings of ECG data. Unscheduled visits will only be presented in the listings.

Reporting of ECG data is described in [Section 11.5](#). Refer to [Section 7.1](#) for handling of decimal values in ECG.

8.1.2.5 Physical Examination Data

Visual assessments to be completed during screening, Week 17 or Week 26 will consist of Snellen and Ishihara testing and will be repeated during the trial if the investigator suspects abnormalities.

Reporting of Physical Examination Data is described in [Section 11.6](#).

Visual assessments will occur at screening, Week 17 (for participants in Arm 1, Arm 2, and Arm 3), or Week 26 (for participants in Arm 4). They will consist of Snellen and Ishihara testing and will be repeated during the trial if the investigator suspects abnormalities.

8.1.2.6 Rate of All-Cause Treatment Discontinuation

All-cause treatment discontinuation will be summarized by treatment arm and overall. Reasons for treatment discontinuation are: adverse event, physician decision, protocol deviation, withdrawal of consent by the participant and other. The “other” category has an “other specify” option, and these reasons, collected in the free text field, will also be tabulated.

All-cause reasons for discontinuation will be listed.

8.2 Secondary Outcome Variables

8.2.1 Secondary Efficacy Variables

The secondary efficacy endpoints are as follows:

Statistical Analysis Plan

Protocol 323-201-00006

- The proportion of participants in each arm who achieve SCC in MGIT by 8 weeks of treatment.
- Time to detection of MGIT cultures.
- The proportion of participants in each arm who convert sputum LAM to negative by 8 weeks of treatment and by end-of-treatment.
- Proportion of participants who develop drug resistance.
- Time to SCC.

8.2.1.1 Sputum Culture Conversion in MGIT by 8 Weeks

The proportion of participants who achieve SCC in MGIT by 8 weeks of treatment will be assessed using the same methods as the primary endpoint. The analysis period is from baseline to the Week 8 visit sputum MGIT culture assessment date.

SCC analyses in MGIT by 8 weeks analysis will be performed using the two MGIT assessments without mitigation (regular). A sensitivity analysis, with and without mitigation analysis (wwom), will be performed using all four samples (two each with and without mitigation).

The statistical analysis for SCC in MGIT by 8 weeks is described in [Section 10.2.1](#)

8.2.1.2 Time to Positivity/Time to Detection of MGIT Cultures

Time to positivity (TTP)/Time to detection of MGIT cultures will be performed using the two MGIT assessments without mitigation. A sensitivity analysis will be performed using all four samples (two each with and without mitigation).

Note that the term “time to positivity” is used interchangeably with the term “time to detection of a positive signal (TTD)”.

The TTP values in Days will be calculated as “days + hours/24” to be used in deriving the analysis values of TTP. If the TTP value is 42 days and x hours, (with $x > 0$) or more than 42 days, (say 44 days), then TTD will be capped at 42 days.

TTP values from MGIT cultures with the following qualitative results will be checked for consistency. For MGIT culture results below, the TTP value should be classified as missing:

- Contaminated
- Positive for MTB complex and contaminated
- No TB growth but positive for other mycobacteria
- Unknown

Statistical Analysis Plan

Protocol 323-201-00006

The TTP value summarized will be derived as follows:

TTP_tabulated = minimum (time to positivity over all records with a non-missing value for TTP for a participant-visit both with and without mitigation).

Baseline TTP will be derived as follows:

Day 1 value = minimum (over all non-missing TTP records for participant-Day 1) [there are 2 records].

Day -1 value = minimum (over all non-missing TTP records for participant-Day -1) [there are 2 records].

Week n value = minimum (over all non-missing TTP records for participant-Week n records) [there will typically be 4 records] for $n \geq 1$.

Similar to baseline values for sputum culture results, for TTP:

Baseline is the Day 1 value (as derived above). If Day 1 is missing, or $TTP \geq 42$ (negative MGIT sputum culture result), then it is the Day -1 values. If both Day 1 and Day -1 values are missing, or $TTP \geq 42$ on both these days, then it is the Week 1 value (as derived above).

The statistical analysis for time to detection of MGIT cultures is described in [Section 10.2.2](#).

8.2.1.3 Sputum Lipoarabinomannan Concentration

Sputum LAM concentrations are measured on up to 3 samples collected at baseline and then at every scheduled visit. Sputum conversion in LAM occurs when a participant has the first of 2 visits of at least 1 week apart with sputum LAM negative (below the lower limit of quantification) and without a positive sputum LAM result in between. The proportion of participants who convert sputum LAM to negative will be assessed at end-of-treatment and at 8 weeks of treatment.

Sputum LAM will be assessed using the same methods as the primary endpoint.

For categorical analyses < 10 pg/mL will be considered Negative. All values ≥ 10 pg/mL will be considered positive. The character result variable will contain “ < 10 ” for values below 10, and the numerical result will be missing for these records.

There are two values for LAM per subject-visit. Only non-missing results will be used. If one is positive, overall result will be positive. Only when both results (or the only result if there is only one) are negative will the result at that visit be negative overall.

Statistical Analysis Plan

Protocol 323-201-00006

SCC for LAM will be considered to have been achieved if there are negative results at two consecutive visits with non-missing results.

LAM values may be analyzed as continuous numerical values.

The statistical analysis for Sputum LAM is described in [Section 10.2.3](#).

8.2.1.4 Drug Resistance

Acquired resistance is defined as a post-baseline resistant result at any time point after a baseline susceptible result. Resistance data is collected for streptomycin, isoniazid, rifampicin, ethambutol, pyrazinamide, bedaquiline and delamanid. The baseline for drug resistance will be Day -1. If Day -1 is missing, then Day 1 will be used. If Day 1 is missing, then Week 1 will be used.

Susceptibility testing (DST) for anti-TB medications will be performed on positive *M tuberculosis* isolates from Day -1 cultures. If Day -1 culture is not positive for *M tuberculosis*, testing will be performed on Day 1 or Week 1 cultures. Susceptibility testing will also be performed on the end-of-treatment sputum specimen, if positive for *M tuberculosis* (Week 17 for Arms 1, 2, and 3, or Week 26 for Arm 4), as well as on positive cultures from participants suspected of relapse. Susceptibility testing may also be performed at other timepoints at the request of the principal investigator or the sponsor.

The presentation of Drug Resistance is described in [Section 10.2.4](#).

MIC testing will be conducted for quabodepistat (OPC-167832). If MIC testing for DBQ and DLM is performed, it will be reported out separately. All MIC testing results will be in a separate report.

8.2.1.5 Time to Sputum Culture Conversion (SCC)

Time to SCC will be calculated using MGIT cultures without the mitigation method measures, i.e., regular (MGIT). A sensitivity analysis will be performed with and without the mitigation method, i.e., MGIT (wwom). Each participant that has converted will have one time to SCC.

If a participant has a positive MGIT culture result throughout the study period, then he/she is considered as not having achieved SCC within the specific period under consideration. The time to SCC in this case is censored (censor variable = 1), and time to SCC will be taken to be from first dose date to end of follow-up (EOT date) or data cut-off date or Week 8 (only for CPC_8 analysis) as applicable in number of days, whichever is earlier. If the participant discontinued from the study, and did not achieve SCC, the time to SCC would be till the date of discontinuation if the date of discontinuation was prior to data cutoff date (DCO), but till DCO if otherwise. If the participant is lost to

Statistical Analysis Plan

Protocol 323-201-00006

follow-up (LTFU), then the time to SCC will be taken till the last MGIT culture assessment date if this is prior to the DCO date, and till the DCO date if the last MGIT culture assessment date is later. Participants who continue on the study beyond DCO, have missing SCC results prior to DCO, and have not achieved SCC within the analytic period, will be censored at their last non-missing SCC assessment date.

If a participant has a negative MGIT culture at 2 consecutive recorded visits more than 1 week apart, then the participant is considered to have had an SCC. The participant must not have a positive MGIT culture result till the end of the analysis period. This time to SCC value is uncensored (censor variable = 0). The time to SCC in this case is the time from first dose date of IMP to the first visit date of the 2 consecutive visit dates at which SCC was observed.

The statistical analysis for time to SCC is described in [Section 10.2.5](#).

8.3 Exploratory Outcome Variables

8.3.1 Exploratory Efficacy Variables

Exploratory efficacy endpoints are:

- The proportion of participants with relapse at 12 months post randomization.
- The proportion of participants with favorable outcome in each experimental arm as compared to the RHEZ standard treatment arm at 6 months post end of treatment and at 12 months post randomization

The statistical analysis for the exploratory efficacy variables is described in [Section 10.3](#).

8.3.1.1 Favorable Outcome

A participant is considered to have a **favorable** outcome if, during the post randomization (post baseline) evaluation period, the participant is alive, completed the post randomization evaluation, is assessable, and otherwise, did not meet the definition of an unfavorable outcome. A participant will not be assessable if he/she does not have any efficacy or safety assessments beyond Week 1.

A participant is considered to have an **unfavorable** outcome if one of the following occurs:

- Clinical progression of pulmonary disease during treatment or the need for an unanticipated surgical intervention for TB (e.g., lobectomy).
- Any growth of *M tuberculosis* from an extrapulmonary site during the post-treatment period (Note: Excludes reinfection with a new strain of *M tuberculosis*).
- Signs and symptoms of active tuberculosis during the follow-up period (i.e., after the end-of-treatment), including radiographic worsening compared to baseline

findings, resulting in re-initiation of anti-mycobacterial therapy (note: excludes a re-initiation that is subsequently found to be due to a misdiagnosis and/or alternative diagnosis).

- Death during treatment or follow-up. This is all-cause death.
- A sputum culture with growth of *M tuberculosis* at certain time points as follows:
 - Failure to achieve SCC at the end of the treatment period that result in a change in anti-mycobacterial therapy.
 - Microbiologic relapse during the follow-up period (i.e., after the end of treatment) (Note: Excludes reinfection and requires more than 1 positive sputum culture with a new strain of *M tuberculosis*).

Favorable outcomes will be determined at the timepoints 12 months post randomization, and at 6 months post-end-of-treatment.

Favorable outcome at 12 months post-randomization is an Investigator-reported assessment and will be reported as collected in the data. The 6-months-post-end of treatment favorable outcomes are derived using the rules specified in [Appendix 8](#).

8.3.1.2 Relapse

To determine if the participant has relapsed or has a new infection of *M tuberculosis*, genotyping will be performed on the baseline culture (Day –1 and/or Day 1, or Week 1, if necessary) and the first of any subsequent positive culture during the post treatment follow-up period. In addition, the sponsor may request genotyping as needed.

Relapse is defined as the same strain of *M tuberculosis* (by genotyping) identified prior to treatment that is causing the recurrence of an active TB disease after a successful treatment (achieved SCC) in a participant. If genotyping identifies an unrelated strain that caused the recurrence, it is considered as a reinfection but not a relapse.

Relapse will be determined at the timepoints 12 months post randomization, and at 6 months post-end-of-treatment.

8.3.2 Exploratory Biomarker Variables

Exploratory biomarker endpoints are:

- Longitudinally assess positron emission tomography/computerized axial tomography (PET/CT) imaging over the course of treatment.
- Longitudinally evaluate the ribosomal ribonucleic acid synthesis ratio (RS ratio) decline in sputum.
- Longitudinally assess whole blood transcriptomic signatures previously associated with TB cure from serum.

Statistical Analysis Plan

Protocol 323-201-00006

The analysis of these exploratory biomarker outcomes will be presented in a separate biomarker report.

9 Disposition and Demographic Analysis

9.1 Participant Disposition

Participant disposition will be summarized by treatment arm and stratification factors (when applicable) for below categories:

- Screened Participants
- Randomized
- Treated
- Randomized and Treated
- Discontinued Treatment
- Discontinued Study
- Completed Treatment
- Completed Study
- Safety analysis set
- mITT analysis set
- PP analysis set
- Treatment completer; Trial completer
- Treatment non-completer; Trial completer
- Treatment completer; Trial non-completer
- Treatment non-completer; Trial non-completer

9.2 Reasons for Discontinuation

Reason for discontinuation of treatment will be summarized by treatment arm and overall.

Reason for Discontinuation from Study will also be summarized by treatment arm and overall.

Statistical Analysis Plan

Protocol 323-201-00006

9.3 Demographic and Baseline Characteristics

Baseline is defined as the last non-missing value obtained at a scheduled visit on or before Day –1.

Demographic and baseline characteristics variables include:

- Age (years)
- Sex (Male/Female)
- Race
- Ethnicity
- TB Treatment History
- TB Treatment History – Site of Disease
- Height (cm)
- Weight (kg)
- BMI (kg/m²)
- HIV Status
- Cavitation status
- Karnofsky Score (%)
- Sputum specimen results (without mitigation)
- Sputum specimen results (with mitigation)

9.4 Medical History

Medical history will be presented by the frequency and proportion (expressed in percent) for each system organ class and preferred term and for each treatment arm. Medical history preferred terms will be coded with MedDRA v25.0 or higher. The summary will be based on the randomized analysis set.

9.5 Treatment Exposure and Compliance

The time and dose of IMP administration during the trial will be recorded in eCRF and be listed. The relative dose intensity (RDI) will be used to assess the treatment compliance. The RDI is defined as:

$$\text{RDI (\%)} = 100 \times \text{ADI (mg/day)} / \text{PDI (mg/day)},$$

where ADI and PDI are the actual dose intensity and planned dose intensity, respectively:

$$\text{PDI (mg/day)} = \text{planned cumulative dose (mg)} / \text{duration of exposure (days)},$$

$$\text{ADI (mg/day)} = \text{actual cumulative dose (mg)} / \text{duration of exposure (days)}.$$

Statistical Analysis Plan

Protocol 323-201-00006

The planned cumulative dose is the planned daily dose amount multiplied by the planned duration of exposure, while the actual cumulative dose is the sum of actual total daily dose amount over the duration of exposure.

The actual total daily dose is the dosage taken during a day by each participant of each of the different IP medications computed separately: delamanid (DLM), bedaquiline (BDQ) and quabodepistat (OPC-167832). The actual total daily dose will need information from Missed Doses, Overdose and Dose Administration.

The Actual Cumulative Dose (ACD) is computed for each participant as the sum of their actual total daily dose over the duration in the study accounting for overdoses and missed doses.

Summary of exposure will be generated for the safety analysis set and include ACD, ADI, PDI and RDI; and RDI categories (>80%, ≤80%; >95%, ≤95%).

The duration of exposure is defined as:

Duration of exposure (days) = (Date of last dose – Date of first dose) + 1, regardless of unplanned intermittent discontinuations. Summary statistics (N, mean, standard deviation, minimum, maximum) will be presented for duration of exposure by treatment arm and overall.

A summary table will be generated for the randomized analysis set presenting descriptive statistics on duration of exposure and the number and percentage of participants with exposure: No exposure, 0 to ≤ 4 Weeks, > 4 to ≤ 8 Weeks, > 8 to ≤ 12 Weeks, 12 to ≤ 16 Weeks, > 16 to ≤ 18 Weeks, > 18 to ≤ 20 Weeks, > 20 to ≤ 25 Weeks, > 25 to ≤ 27 Weeks, > 27 Weeks.

A listing will be generated for exposure information.

9.6 Prior and Concomitant Medication

The frequency and proportion (expressed as percent) of participants taking concomitant medications will be tabulated by drug classification using the WHO drug dictionary WHODRUG B3G Mar 2023 (or newer version) for safety analysis set Medications taken prior to the study medication treatment period, concomitant medications taken during study medication treatment period and medications taken after the study treatment period, will be tabulated. The study medication treatment period is defined as day of first IMP treatment to the last day of IMP treatment. “After” study treatment refers to the period following the last day of IMP treatment to the end of the follow-up period. In instances where a participant may be followed up for a longer time beyond the 1-year post

Statistical Analysis Plan

Protocol 323-201-00006

randomization end of study, all medications taken in this period will also be included in the “after” study treatment period.

Prior medications that are not Anti-TB medications were collected for only 30 days prior to the first screening visit, while prior Anti-TB medications were those used at any time before starting study treatment.

The proportion of participants taking medications will be tabulated for all safety analysis sets prior to trial medication. The proportion of participants taking concomitant medications will be tabulated for the safety analysis set during and after the trial medication. Anti-TB concomitant medications and other general concomitant medications will be summarized separately.

In addition, listings of concomitant medications will be provided.

9.7 Rescue Treatment/Medications

Rescue treatment consisting of the standard of care treatment, i.e., RHEZ is provided in the following circumstances:

- 1) If a participant is sputum culture positive for *M tuberculosis* at the end of treatment,
- 2) If a participant has a microbiologic relapse subsequent to the end of treatment, or
- 3) If, in the opinion of the investigator, a participant is clinically deteriorating, based on any combination of signs, symptoms, or chest radiograph data.

Note: Standardized rescue treatment consisting of RHEZ is to be used for Arm 1, Arm 2, and Arm 3 not responding to therapy. However, participants in Arm 4 will receive individualized care according to local guidelines.

The frequency and proportion (expressed as percent) of participants taking rescue medications will be tabulated in the safety analysis set.

A listing will display all rescue medications used in the study along with the reason for rescue medication.

9.8 Protocol Deviations

Major protocol deviations are entered into the CRF. These will be summarized by type of deviations (e.g., deviations in entry criteria, dosing, concomitant medication, procedural, etc.) by site. In addition, a listing of the major protocol deviations will be provided.

10 Efficacy Analyses

10.1 Primary Efficacy Analyses

The primary efficacy analysis will be based on the mITT population for (regular) MGIT. The primary efficacy endpoint of the trial is the proportion of participants who have achieved SCC by the end of treatment. SCC occurs when a participant has the first of 2 visits of at least 1 week apart with sputum cultures negative and without a positive sputum culture result in between, and without a positive culture by the end of treatment. If there are missing or contaminated culture results between two negative sputum culture assessments, the definition of conversion is still met.

Participants who discontinue treatment but continue to remain on the study will be included in this analysis.

The arms 1, 2 and 3 will be pooled. Noninferiority with RHEZ will be established if the lower limit of the 80% CI for the difference of proportion of participants with SCC in the pooled arms 1, 2 and 3, and the proportion of participants in the RHEZ arm, is larger than -0.12 . In addition, each treatment arm will be compared separately to RHEZ.

The Miettinen and Nurminen method will be used to obtain the 80% CI of difference of proportions.

The SAS code for this analysis is provided in [Appendix 7 SAS Code](#)

The 80% and 95% CIs of the proportion difference between each arm and the standard-of-care arm, RHEZ, will be provided. In addition, Cochran-Armitage test will be used to detect trend in proportion of SCC with increasing quabodepistat (OPC-167832) dose.

Descriptive analyses will be conducted on the primary efficacy endpoint on the CPC analysis set and PP analysis sets.

For the CPC analysis, only completers and potential completers are included in the analysis. Participants ongoing treatment at data cutoff, will be excluded from the analysis. The proportion of participants achieving SCC within each treatment arm, pooled over OPC-167832 arms, and overall will be tabulated. No imputation is applied for potential completers, SCC is determined based on available assessments only. For completers, the end of treatment visit must be prior to or on the data cutoff date. For participants who achieve SCC within the analysis period (from first dose date to last dose date), SCC is set to “Yes”. For participants who do not achieve SCC within the analysis period, but for whom the last non-missing assessment within this period is negative, SCC will be determined by taking into account a next available visit assessment after the last non-missing on-treatment assessment, allowing for SCC to occur prior to or on data

Statistical Analysis Plan

Protocol 323-201-00006

cutoff. The denominator will be all CPC participants, and the numerator will be the number of participants achieving SCC (SCC = Yes), expressed as a percentage among CPC participants.

A sensitivity analysis will be conducted on the primary efficacy endpoint on the mITT analysis set using sputum culture assessments from both with and without mitigation (wwom) MGIT cultures similar to the regular MGIT analyses described above.

10.2 Secondary Efficacy Analyses

The secondary efficacy endpoints of this protocol are as stated in [Section 8.2.1](#).

10.2.1 Sputum Culture Conversion in MGIT by 8 Weeks

The same analysis methodology specified for the primary endpoint will be presented for the secondary endpoint of SCC by 8 weeks.

10.2.2 Time to Positivity/Time to Detection of MGIT Cultures

Time to positivity/Time to detection of MGIT cultures and change from baseline will be summarized by treatment arm and visit, for each stratum separately and overall. This summary will be generated for the two populations, CPC analysis set and mITT analysis set. A separate sensitivity analysis will be conducted for TTP for with and without the mitigation method cultures.

10.2.3 Sputum Lipoarabinomannan

Numeric LAM data will be converted to a binary variable using the rule: if the LAM result is less than 10 pg/mL then it is interpreted as a negative result. If a LAM result is greater than or equal to 10 pg/mL then it is interpreted as positive result. Refer to [Section 8.2.1.3](#). Sputum LAM conversion (SLC) will be assessed using the same definitions and rules as for SCC. The proportion of participants in each arm who convert sputum LAM to negative (i.e., achieve SLC) by 8 weeks of treatment and by the end of treatment will be analyzed and presented following the same methods as for SCC.

If data comes in character format “<10” with the corresponding numeric value missing, then the character format “<10” will be interpreted as a numeric value less than 10 pg/mL.

10.2.4 Drug Resistance

The number and proportion of participants who develop resistance to each of streptomycin, isoniazid, rifampicin, ethambutol, pyrazinamide, and bedaquiline will be

Statistical Analysis Plan

Protocol 323-201-00006

tabulated. Resistance data for streptomycin, isoniazid, rifampicin, ethambutol, pyrazinamide and bedaquiline is collected in the CRF and will be reported as collected for both the mITT analysis set and for the safety analysis set. by stratification variables and overall. Resistance results for each IMP will be presented by visit and overall. If a participant developed resistance to an IMP at scheduled or unscheduled timepoint, then they will be reported as having developed resistance overall within the study period.

10.2.5 Time to Sputum Conversion

For the final analysis, time to SCC will be presented on the mITT analysis set. CC

[REDACTED]. The time to SCC analysis will be performed on both the regular and wwom MGIT data.

Censoring for the time to SCC endpoint has been described in [Section 8.2.1.5](#).

Time to SCC will be analyzed using the Kaplan-Meier (KM) method. KM time to SCC curves for each treatment arm will be presented graphically and median time (displayed in days) to conversion will be estimated and presented together with the 25th and 75th percentiles. The Participants at risk will be summarized by treatment group at Week 2 (Day 14), Week 4 (Day 28), Week 6 (Day 42), Week 8 (Day 56), Week 10 (Day 70), Week 15 (Day 105), Week 17 (Day 119), Week 23 (Day 161) and Week 26 (Day 182).

Summaries of the number and percentage of participants experiencing an event, and number and percentage of participants censored, will be provided for each treatment group.

For both end of treatment and 8-weeks analyses, listings will be produced, including whether the participant had the event or, date of event/censored date, reasons for censoring, the start date, and the time to event (days).

10.3 Exploratory Efficacy Analyses

The exploratory efficacy endpoints of this protocol are:

- The proportion of participants with favorable outcome (FO) in each experimental arm vs RHEZ arm at 6 months post end of treatment and 12 months post randomization.
 - FO and unfavorable outcome will be presented by frequency and proportion (expressed as percent) by treatment arm, pooled treatment arm, and overall, and by strata. 80% and 95% CIs will be presented for the estimated proportions, for each arm, and for the pooled delamanid, bedaquiline,

OPC-167832 (quabodepistat) (DBO) arms. Participants will be deemed not assessable for a favorable or unfavorable outcome if they do not have any efficacy or safety assessments beyond Week 1. Not assessable participants will not appear in the denominator or the numerator.

- the difference in FO proportions in the DBO arms vs RHEZ will be explored. Differences versus RHEZ, and Miettinen-Nurminen 80% and 95% CIs will be presented for each arm, and for the pooled DBO arms.
- the frequency and proportion (expressed as percent) of the occurrence of each component of the composite FO outcome (favorable, unfavorable, not assessable) will be tabulated, by treatment arm, pooled treatment arm, and strata.
- The proportion of participants with relapse at the timepoints 6 months post end of treatment and 12 months post randomization along with criteria for relapse.
 - the frequency and proportion (expressed as percent) of the occurrence of relapse by the 12-month post randomization timepoint will be tabulated, by treatment arm, pooled treatment arm, overall, and by strata.

A participant achieves an unfavorable outcome prior to 6-months post-end-of-treatment if the date of detection of unfavorable outcome is prior to the 6-months post-end-of-treatment date.

For determination of favorable outcome at 52 weeks (12 months post randomization), Investigator assessments overall, and for each criterion, will be tabulated.

Genotyping data will be used to assess relapse or reinfection. The genotype result captured in the CRF as “relapse” will be tabulated.

The number and proportion (expressed as percent) of participants experiencing a relapse will be tabulated. Differences for proportion relapsing as compared to the RHEZ group will be calculated, and Miettinen-Nurminen 80% and 95% CIs will be presented.

10.4 Exploratory Biomarker Analyses

The exploratory biomarkers specified in [Section 8.3.2](#) will be described and analysed in a separate report.

10.5 Sensitivity Analyses

Sensitivity analyses have been described in various sections above. They are also summarized below:

- The PP analysis set will be used for sensitivity analyses of select efficacy data.

Statistical Analysis Plan

Protocol 323-201-00006

- For the primary endpoint, sensitivity analyses for determination of SCC may be performed for the **CI**. Sensitivity analysis of the primary endpoint will be performed using all 4 samples (wwom).
- Sensitivity analysis of TTP and Time to SCC will be performed using all 4 samples (wwom).

Select sensitivity analyses may be performed for the **CI**.

10.6 Subgroup Analyses

Subgroup analyses may be conducted.

11 Safety Analyses

Safety endpoints will be summarized using descriptive statistics (number, median, mean, standard deviation, minimum, maximum) for continuous values, and by frequency and proportion (expressed as percent) for discrete variables. Frequency and proportion (expressed as percent) of AEs and clinical laboratory test results by severity and toxicity grades will be presented.

11.1 Extent of Exposure

Extent of exposure to the trial medication for safety analysis set will be summarized using descriptive statistics (n, percentage) by treatment arm, pooled treatment arm and overall.

For each participant, duration of exposure to study drug will be defined as (date of last dose – date of first dose + 1). Participants' total days of exposure is defined as the sum of the number of exposure days for all participants within a group. Total days of exposure will be presented by treatment arm and overall.

11.2 Adverse Events

The frequency and percentage or proportion of participants with the following events will be summarized and tabulated by SOC, MedDRA preferred term, severity and treatment arm:

- AEs
- TEAEs
- Severe TEAEs
- TEAEs by DAIDS grade where grade ≥ 3
- TEAEs related to IMP
- TEAEs Leading to death

Statistical Analysis Plan

Protocol 323-201-00006

- Serious AEs
- Serious TEAEs
- TEAEs Leading to Discontinuations

The total number of AEs in each of these categories will be summarized.

All AEs will be presented in a listing. The listing of death due to AE, serious AE and TEAE leading to discontinuation will also be provided. In addition, the frequency and percentage or proportion of TEAE incidences will be summarized for serious TEAE, serious study medication related TEAE and non-serious TEAE.

11.3 Clinical Laboratory Data

Clinical laboratory test parameters and mean changes from baseline will be summarized by treatment arm for each scheduled visit. The incidence of potentially clinically significant (PCS) changes and abnormalities in clinical laboratory test parameters will be summarized using the DAIDS criteria (all grades greater than or equal to 1). The PCS events will include unscheduled assessments. Clinical laboratory test data will be presented in listings. For laboratory tests with different ranges for males and females, the results will be presented both separately by sex, and combined, in the Tables.

Unscheduled laboratory assessments will be listed.

Laboratory data will be presented in SI units. Laboratory values that are received in character format with the corresponding numeric format missing, will be reviewed and assigned a numeric value for using in generating the summary tables.

11.4 Vital Sign Data

Vital sign parameters and mean changes from baseline will be summarized by treatment arm for each scheduled visit.

The incidence of potentially clinically significant changes and abnormalities in vital sign parameters will be summarized. Data from all visits will be included in the clinically significant result tables and included in all listings.

The DAIDS table criteria will be used for identifying vital signs of potential clinical significance and these values will be tabulated. These will be all values assigned a DAIDs grade greater than or equal to 1. The sponsor provided criteria from [Appendix 3 Sponsor Provided Criteria for Identifying Vital Sign Measurements of Potential Clinical Relevance](#) will also be tabulated separately.

Multiple numerical vital sign examination results for the same visit will be averaged to present a single value at a particular visit. Vital sign examinations marked by the investigator as repeat examinations will replace original results.

Unscheduled vital sign examinations will not enter summary tables and will only be reported in listings. However, unscheduled vital sign data determined to be potentially clinically relevant (PCR) will be summarized in the table for PCR vital signs.

11.5 Electrocardiogram Data

Electrocardiogram measurements and mean changes from baseline will be summarized by treatment over all scheduled visits. The following ECG parameters will be collected: ECG Mean Heart Rate (Beats/Min), PR Interval (msec), QRS Duration (msec), QT Interval (msec), QTcB Interval (msec), QTcF Interval (msec), RR Interval (msec). The average of triplicate ECGs will be presented rounded to the nearest integer. Refer to [Section 8.1.2.4](#) for details.

Electrocardiogram data will be presented in listings. Both scheduled and unscheduled visit assessments will be listed. Potentially clinically significant ECG findings will be identified using the sponsor defined criteria in [Appendix 4 Sponsor Provided Criteria for Identifying ECG Measurements of Potential Clinical Relevance](#)

and will also be summarized.

11.6 Physical Examination Data

Physical examination findings for HEENT (head, eyes, ears, nose, and throat), Thorax, Abdomen, Skin and Mucosae, Neurological, Extremities, and Urogenital will be listed by participant for all visits including unscheduled. Clinical Significance assessments will be included in the listing on physical examination.

A listing of visual assessment based on Snellen and Ishihara testing will be presented.

11.7 Clinical Signs and Symptoms of Tuberculosis

An aggregate of clinical signs and symptoms of pulmonary TB will be assessed at screening and throughout the trial. Signs and symptoms will be assessed by the investigator (cough, hemoptysis, dyspnea, chest pain, loss of appetite, feeling feverish, and night sweats); from vital signs (body temperature, respiratory rate and heart rate), and physical examination (including weight and body mass index) from clinical laboratory tests (hemoglobin, hematocrit, c-reactive protein, and serum albumin); and from chest radiograph. A chest radiograph must be taken during the screening period, and an official interpretation must be available, and the assessment of its compatibility with pulmonary

Statistical Analysis Plan

Protocol 323-201-00006

TB must be made, prior to randomization. An end of treatment chest radiograph will be taken at Week 17 (for participants in Arms 1, 2, and 3) or Week 26 (for participants in Arm 4) and at Month 12.

A summary table will present the number and percent of participants with: persistent cough, fever, weight loss, findings on recent chest radiograph consistent with TB, hemoptysis, dyspnea, chest pain, night sweats and loss of appetite.

A listing will display individual participant data including those recording other signs and symptoms.

11.8 Other Safety Data

There are no other safety data to be analyzed.

CCI

13 Pharmacogenomic Analyses

The assessment of transcriptomic signatures previously associated with TB cure from serum will be included as a part of Exploratory Biomarker Analyses as described earlier. No other pharmacogenomic analyses will be conducted.

14 Bioavailability Analyses

There will be no bioavailability analyses in this trial.

CCI

CCI

16 Data Monitoring Committee Analyses

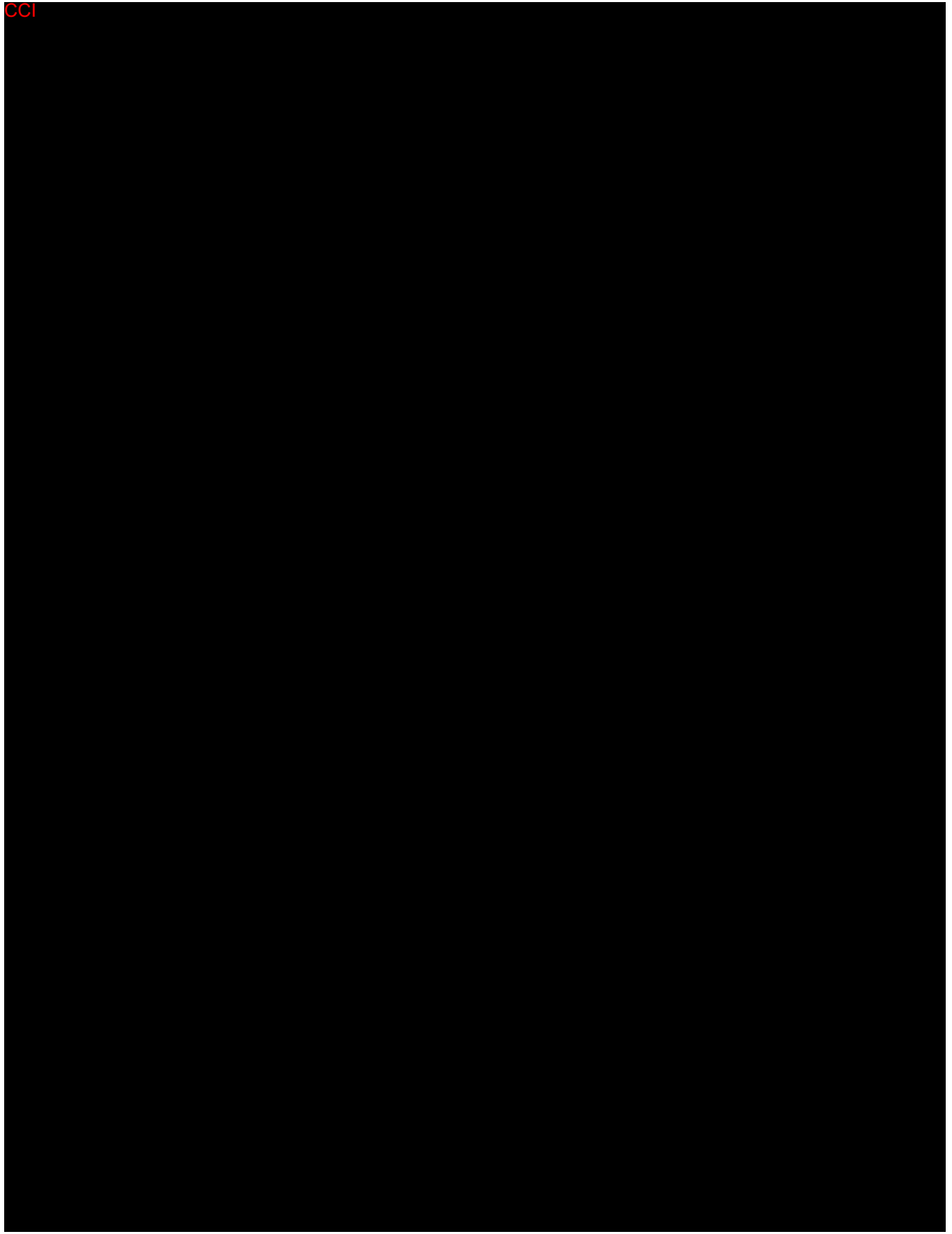
An independent Data Monitoring Committee (DMC) will be contracted by Otsuka to review safety and efficacy data during the conduct of the trial. The DMC will convene and operate based on an established charter; the schedule of DMC review and contents/scope of DMC reports are discussed in the DMC charter.

The DMC will be permitted to seek additional independent expertise, as needed. The primary responsibility of the DMC will be to monitor safety and to advise the sponsor of the clinical project regarding whether or not the safety concerns merit stopping the trial. Towards this objective, the DMC will meet on a predetermined schedule to review safety and available efficacy data. The DMC and the study team will decide on the list of outputs that the DMC will review, and these will be presented at each DMC meeting.

17 Changes in Planned Analysis

Not applicable.

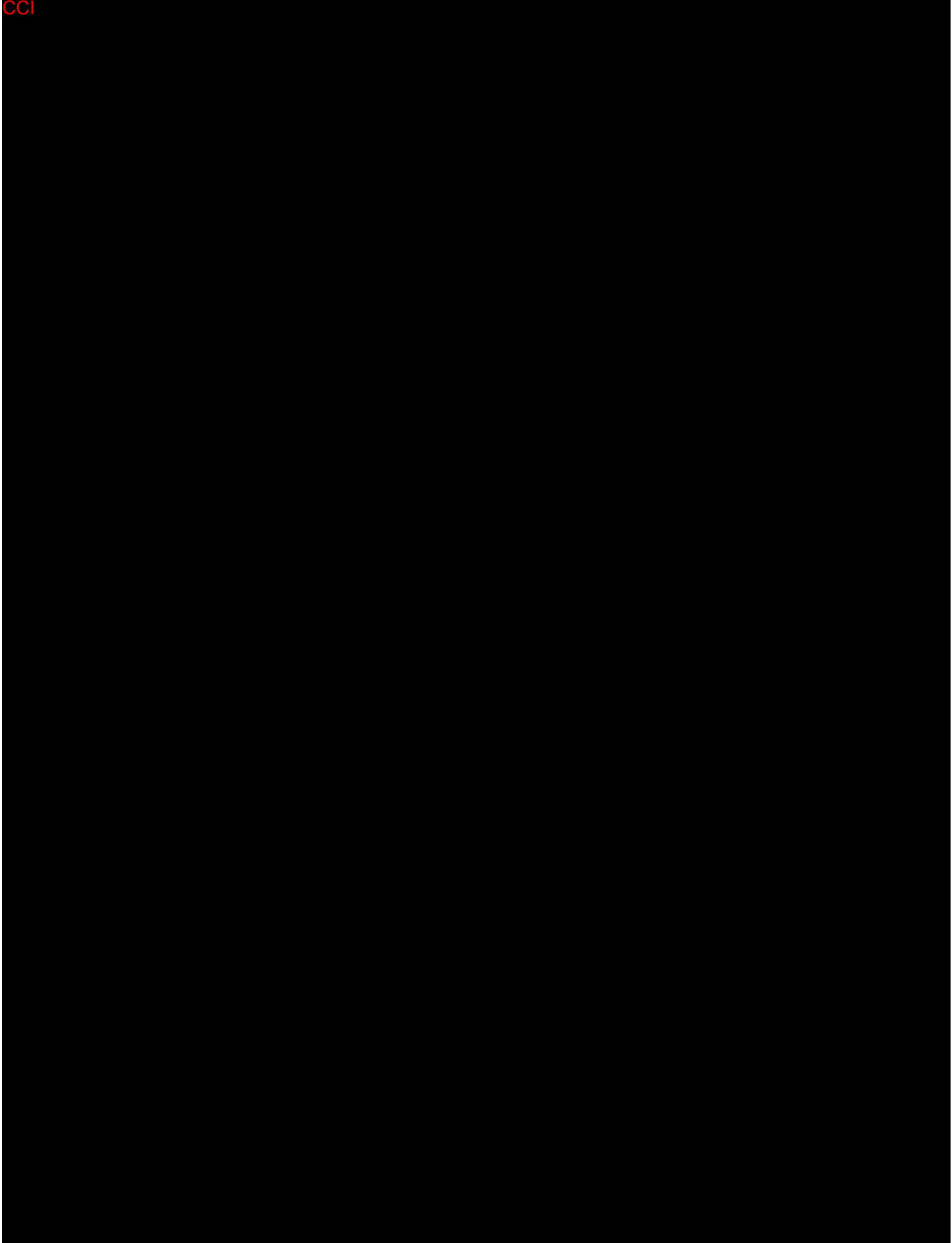
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Statistical Analysis Plan

Protocol 323-201-00006

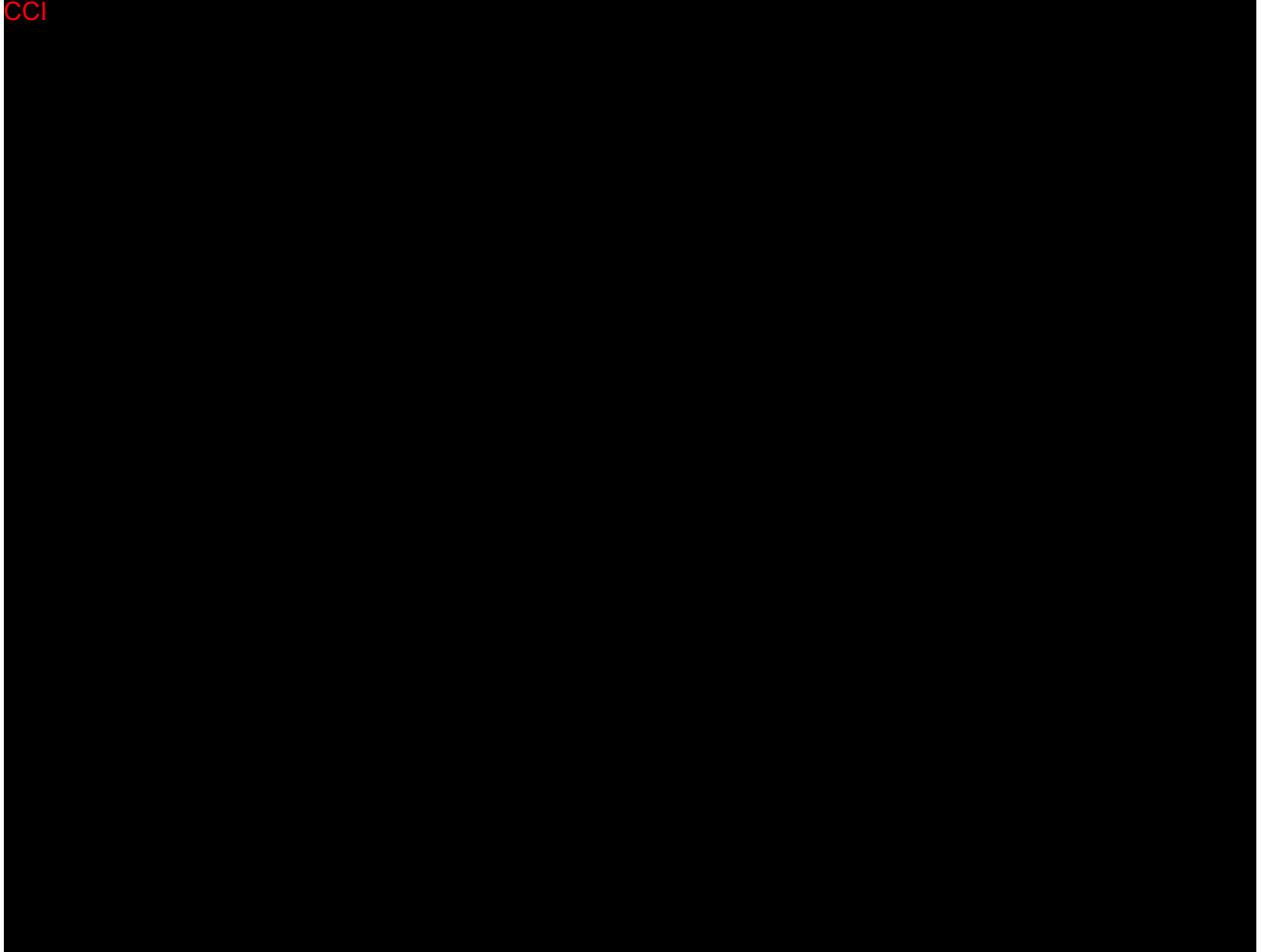
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Statistical Analysis Plan

Protocol 323-201-00006

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Statistical Analysis Plan

Protocol 323-201-00006

19 References

- ¹ United States Department of Health and Human Services, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events; 2017.

Statistical Analysis Plan

Protocol 323-201-00006

20 Appendices

Appendix 1 Definition of Grades in Serum Chemistry, Hematology and Urinalysis Lab Test Results in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

The table below contains some of the criteria provided in the DAIDS table. Please see pages 25-31 of the DAIDS v2.1 tables¹ for the complete list for Chemistry, Hematology, and Urinalysis.

Definition of Grades in Serum Chemistry, Hematology and Urinalysis Lab Test Results in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events								
LAB GROUP	TEST	UNITS	SEX	AGE GROUP	GRADE 1 MILD	GRADE 2 MODERATE	Clinically Significant	
							GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Chemistry	Albumin, Low	g/dL	Male/Female	All	3.0 to < LLN	≥ 2.0 to < 3.0	< 2.0	NA
Chemistry	Albumin, Low	g/L	Male/Female	All	30 to < LLN	≥ 20 to < 30	< 20	NA
Chemistry	Alkaline Phosphatase, High	-	Male/Female	All	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Chemistry	ALT or SGPT, High	-	Male/Female	All	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Chemistry	AST or SGOT, High	-	Male/Female	All	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Chemistry	Total Bilirubin, High	-	Male/Female	> 28 days of age	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN
Chemistry	Calcium, High	mg/dL	Male/Female	≥ 7 days of age	10.6 to < 11.5	11.5 to < 12.5	12.5 to < 13.5	≥ 13.5
Chemistry	Calcium, High	mmol/L	Male/Female	≥ 7 days of age	2.65 to < 2.88	2.88 to < 3.13	3.13 to < 3.38	≥ 3.38
Chemistry	Calcium, Low	mg/dL	Male/Female	≥ 7 days of age	7.8 to < 8.4	7.0 to < 7.8	6.1 to < 7.0	< 6.1
Chemistry	Calcium, Low	mmol/L	Male/Female	≥ 7 days of age	1.95 to < 2.10	1.75 to < 1.95	1.53 to < 1.75	< 1.53
Chemistry	Creatinine, High	-	Male/Female	All	1.1 to 1.3 × ULN	> 1.3 to 1.8 × ULN	> 1.8 to < 3.5 × ULN	≥ 3.5 × ULN
Chemistry	Creatinine Clearance or eGFR, Low	ml/min or ml/min/1.73m ²	Male/Female	All	N/A	< 90 to 60 ml/min or ml/min/1.73 m ² OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m ² OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m ² OR ≥ 50% decrease from participant's baseline or dialysis needed

Definition of Grades in Serum Chemistry, Hematology and Urinalysis Lab Test Results in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events								
LAB GROUP	TEST	UNITS	SEX	AGE GROUP	GRADE 1 MILD	GRADE 2 MODERATE	Clinically Significant	
							GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Chemistry	Glucose, Fasting, High	mg/dL	Male/Female	All	110 to 125	> 125 to 250	> 250 to 500	≥ 500
Chemistry	Glucose, Fasting, High	mmol/L	Male/Female	All	6.11 to < 6.95	6.95 to < 13.89	13.89 to < 27.75	≥ 27.75
Chemistry	Glucose, Fasting, Low	mg/dL	Male/Female	≥ 1 month of age	55 to 64	40 to < 55	30 to < 40	< 30
Chemistry	Glucose, Fasting, Low	mmol/L	Male/Female	≥ 1 month of age	3.05 to < 3.55	2.22 to < 3.05	1.67 to < 2.22	< 1.67
Chemistry	Glucose, Non Fasting, High	mg/dL	Male/Female	All	116 to 160	> 160 to 250	> 250 to 500	≥ 500
Chemistry	Glucose, Non Fasting, High	mmol/L	Male/Female	All	6.44 to < 8.89	8.89 to < 13.89	13.89 to < 27.75	≥ 27.75
Chemistry	Cholesterol, High	mg/dL	Male/Female	All	200 to < 240	240 to < 300	≥ 300	NA
Chemistry	Cholesterol, High	mmol/L	Male/Female	All	5.18 to < 6.19	6.19 to < 7.77	≥ 7.77	NA
Chemistry	Inorganic Phosphorus, Low	mg/dL	Male/Female	> 14 years of age	2.0 to < LLN	1.4 to < 2.0	1.0 to < 1.4	< 1.0
Chemistry	Inorganic Phosphorus, Low	mmol/L	Male/Female	> 14 years of age	0.65 to < LLN	0.45 to < 0.65	0.32 to < 0.45	< 0.32
Chemistry	Inorganic Phosphorus, Low	mg/dL	Male/Female	< 1 to 14 years of age	3.0 to < 3.5	2.5 to < 3.0	1.5 to < 2.5	< 1.5
Chemistry	Inorganic Phosphorus, Low	mmol/L	Male/Female	< 1 to 14 years of age	0.97 to < 1.13	0.81 to < 0.97	0.48 to < 0.81	< 0.48
Chemistry	Magnesium, Low	mEq/L	Male/Female	All	1.2 to < 1.4	0.9 to < 1.2	0.6 to < 0.9	< 0.6
Chemistry	Magnesium, Low	mmol/L	Male/Female	All	0.60 to < 0.70	0.45 to < 0.60	0.30 to < 0.45	< 0.30
Chemistry	Potassium, High	mEq/L	Male/Female	All	5.6 to < 6.0	6.0 to < 6.5	6.5 to < 7.0	≥ 7.0
Chemistry	Potassium, High	mmol/L	Male/Female	All	5.6 to < 6.0	6.0 to < 6.5	6.5 to < 7.0	≥ 7.0
Chemistry	Potassium, Low	mEq/L	Male/Female	All	3.0 to < 3.4	2.5 to < 3.0	2.0 to < 2.5	< 2.0
Chemistry	Potassium, Low	mmol/L	Male/Female	All	3.0 to < 3.4	2.5 to < 3.0	2.0 to < 2.5	< 2.0
Chemistry	Sodium, High	mEq/L	Male/Female	All	146 to < 150	150 to < 154	154 to < 160	≥ 160
Chemistry	Sodium, High	mmol/L	Male/Female	All	146 to < 150	150 to < 154	154 to < 160	≥ 160
Chemistry	Sodium, Low	mEq/L	Male/Female	All	130 to < 135	125 to < 130	121 to < 125	≤ 120
Chemistry	Sodium, Low	mmol/L	Male/Female	All	130 to < 135	125 to < 130	121 to < 125	≤ 120
Chemistry	Triglycerides, High	mg/dL	Male/Female	All	150 to 300	> 300 to 500	> 500 to < 1,000	> 1,000
Chemistry	Triglycerides, High	mmol/L	Male/Female	All	1.71 to 3.42	> 3.42 to 5.7	> 5.7 to 11.4	> 11.4
Chemistry	Uric Acid, High	mg/dL	Male/Female	All	7.5 to < 10.0	10.0 to < 12.0	12.0 to < 15.0	≥ 15.0

Definition of Grades in Serum Chemistry, Hematology and Urinalysis Lab Test Results in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events								
LAB GROUP	TEST	UNITS	SEX	AGE GROUP	GRADE 1 MILD	GRADE 2 MODERATE	Clinically Significant	
							GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Chemistry	Uric Acid, High	mmol/L	Male/Female	All	0.45 to < 0.59	0.59 to < 0.71	0.71 to < 0.89	≥ 0.89
Hematology	Activated Partial Thromboplastin Time, High	-	Male/Female	All	1.1 to < 1.66 × ULN	1.66 to < 2.33 × ULN	2.33 to < 3.00 × ULN	≥ 3.00 × ULN
Hematology	Prothrombin Time, High	-	Male/Female	All	1.1 to < 1.25 × ULN	1.25 to < 1.50 × ULN	1.50 to < 3.00 × ULN	≥ 3.00 × ULN
Hematology	Partial Thromboplastin Time, High	-	Male/Female	All	1.1 to < 1.66 × ULN	1.66 to < 2.33 × ULN	2.33 to < 3.00 × ULN	≥ 3.00 × ULN
Hematology	International Normalized Ratio (INR), High	-	Male/Female	All	1.1 to < 1.5 × ULN	1.5 to < 2.0 × ULN	2.0 to < 3.0 × ULN	≥ 3.00 × ULN
Hematology	Absolute CD4+ Count, Low	cell/mm ³	Male/Female	> 5 years of age (not HIV infected)	300 to < 400	200 to < 300	100 to < 200	< 100
Hematology	Absolute CD4+ Count, Low	cells/L	Male/Female	> 5 years of age (not HIV infected)	300 to < 400	200 to < 300	100 to < 200	< 100
Hematology	Absolute Lymphocytes, Low	cell/mm ³	Male/Female	> 5 years of age (not HIV infected)	600 to < 650	500 to < 600	350 to < 500	< 350
Hematology	Absolute Lymphocytes, Low	cells/L	Male/Female	> 5 years of age (not HIV infected)	0.600 × 10 ⁹ to < 0.650 × 10 ⁹	0.500 × 10 ⁹ to < 0.600 × 10 ⁹	0.350 × 10 ⁹ to < 0.500 × 10 ⁹	< 0.350 × 10 ⁹
Hematology	Absolute Neutrophil Count, Low	cell/mm ³	Male/Female	> 7 days of age	800 to 1,000	600 to 799	400 to 599	< 400
Hematology	Absolute Neutrophil Count, Low	cells/L	Male/Female	> 7 days of age	0.800 × 10 ⁹ to 1,000 × 10 ⁹	0.600 × 10 ⁹ to 0.799 × 10 ⁹	0.400 × 10 ⁹ to < 0.599 × 10 ⁹	< 0.400 × 10 ⁹
Hematology	Hemoglobin, Low	g/dL	Male	≥ 13 years of age	10.0 to 10.9	9.0 to < 10.0	7.0 to < 9.0	< 7.0
Hematology	Hemoglobin, Low	mmol/L	Male	≥ 13 years of age	6.19 to 6.76	5.57 to < 6.19	4.34 to < 5.57	< 4.34
Hematology	Hemoglobin, Low	g/dL	Female	≥ 13 years of age	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
Hematology	Hemoglobin, Low	mmol/L	Female	≥ 13 years of age	5.88 to 6.48	5.25 to < 5.88	4.03 to < 5.25	< 4.03
Hematology	Hemoglobin, Low	g/dL	Male/Female	57 days of age to < 13 years of age	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5

Statistical Analysis Plan

Protocol 323-201-00006

Definition of Grades in Serum Chemistry, Hematology and Urinalysis Lab Test Results in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events								
LAB GROUP	TEST	UNITS	SEX	AGE GROUP	GRADE 1 MILD	GRADE 2 MODERATE	Clinically Significant	
							GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Hematology	Hemoglobin, Low	mmol/L	Male/Female	57 days of age to < 13 years of age	5.88 to 6.48	5.25 to < 5.88	4.03 to < 5.25	< 4.03
Hematology	Platelet Count, Decreased	cells/mm ³	Male/Female	All	100,000 to < 125,000	50,000 to < 100,000	25,000 to < 50,000	< 25,000
Hematology	Platelet Count, Decreased	cells/L	Male/Female	All	100,000 × 10 ⁹ to < 125,000 × 10 ⁹	50,000 × 10 ⁹ to < 100,000 × 10 ⁹	25,000 × 10 ⁹ to < 50,000 × 10 ⁹	< 25,000 × 10 ⁹
Hematology	White Blood Cell, Decreased	cells/mm ³	Male/Female	> 7 days of age	2,000 to 2,499	1,500 to 1,999	1,000 to 1,499	< 1,000
Hematology	White Blood Cell, Decreased	cells/L	Male/Female	> 7 days of age	2,000 × 10 ⁹ to 2,499 × 10 ⁹	1,500 × 10 ⁹ to 1,999 × 10 ⁹	1,000 × 10 ⁹ to 1,499 × 10 ⁹	< 1,000 × 10 ⁹
Urinalysis	Urine Glucose	-	Male/Female	All	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Urinalysis	Urine Blood	-	Male/Female	All	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross OR Presence of RBC casts OR Intervention indicated	Life-threatening consequences
Urinalysis	Urine Protein	-	Male/Female	All	1+	2+	3+ or higher	NA

LLN = lower limit of normal; NA = not applicable; RBC = red blood cell; ULN=upper limit of normal

Appendix 2 Definition of Grades for Vital Signs in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

The table below contains some of the criteria provided in the DAIDS table. Please see pages of the DAIDS v2.1 tables¹ for blood pressure abnormalities (page 7), unintentional weight loss (page 27), fever (page 21).

Definition of Grades for Vital Sign in the DAIDS Table for Grading the Severity of Adult Adverse Events					
Abnormality	AGE GROUP	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Hypertension (with the lowest reading taken after repeat testing during a visit) Male/Female	≥ 18 years of age	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated

Definition of Grades for Vital Sign in the DAIDS Table for Grading the Severity of Pediatric Adverse Events				
Abnormality	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5% to < 9% loss in body weight from baseline	≥ 9% to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Fever (non-axillary temperatures only)	38.0°C to < 38.6°C or 100.4°F to < 101.5°F	≥ 38.6°C to < 39.3°C or ≥ 101.5°F to < 102.7°F	≥ 39.3°C to < 40.0°C or ≥ 102.7°F to < 104.0°F	≥ 40.0°C or ≥ 104.0°F

Statistical Analysis Plan

Protocol 323-201-00006

Appendix 3 Sponsor Provided Criteria for Identifying Vital Sign Measurements of Potential Clinical Relevance

Sponsor Provided Criteria for Identifying Vital Sign Measurements of Potential Clinical Relevance		
Variable	PCR Criterion Value	Change Relative to Baseline
Systolic BP	> 160 mmHg	> 20 mmHg increase
	< 90 mmHg	> 20 mmHg decrease
Diastolic BP	≥ 100 mmHg	> 15 mmHg increase
	< 50 mmHg	> 15 mmHg decrease
Heart Rate	> 120 bpm	> 15 bpm increase
	< 50 bpm	> 15 bpm decrease
Respiratory Rate	≥ 25 breaths/min	-
	< 12 breaths/min	-
Temperature	< 35°C	-
	> 38.0°C	-
Weight	-	> 5% increase
	-	> 5% decrease

Statistical Analysis Plan

Protocol 323-201-00006

Appendix 4 Sponsor Provided Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Sponsor Provided Criteria for Identifying EC Measurements of Potential Clinical Relevance		
Category	Criterion Value ^a	Change Relative to Baseline ^a
Diagnosis		
Interval		
RR High	> 1200 msec	
RR Low	< 600 msec	
Rhythm		
Sinus tachycardia ^b	(HR_Mean > 100) AND (PR_Mean is Not Null)	
Sinus tachycardia ^b	(HR_Mean > 119) and (PR_Mean is Not Null)	
Sinus bradycardia ^c	(HR_Mean < 50 bpm) and (PR_Mean is Not Null)	
Sinus bradycardia ^c	(HR_Mean < 41) and (PR_Mean is Not Null)	
Artificial Pacemaker	All	not present → present
Atrial fibrillation	All	not present → present
Atrial flutter	All	not present → present
Atrial Pacing	All	not present → present
Atrial Tachycardia	All	not present → present
Ectopic Supraventricular Rhythm	All	not present → present
Idioventricular Rhythm	All	not present → present
Junctional Rhythm	All	not present → present
Junctional Tachycardia	All	not present → present
Sinus Pauses	All	not present → present
Sinus Bradycardia	All	not present → present
Sinus Tachycardia	All	not present → present
Supraventricular tachycardia	All	not present → present
Ventricular Fibrillation	All	not present → present
Other	All	not present → present
Ectopy	All	not present → present
Atrial Bigeminy	All	not present → present
Atrial Premature Complexes	All	not present → present
Frequent Atrial Premature Complexes (>3)	All	not present → present
Ventricular Premature Complexes	All	not present → present
Frequent Ventricular Premature Complexes (>2)	All	not present → present
Ventricular Bigeminy	All	not present → present
Ventricular Couplets	All	not present → present

Statistical Analysis Plan

Protocol 323-201-00006

Sponsor Provided Criteria for Identifying EC Measurements of Potential Clinical Relevance		
Category	Criterion Value^a	Change Relative to Baseline^a
Diagnosis		
Ventricular Trigeminy	All	not present → present
Non-sustained Ventricular Tachycardia	All	not present → present
Premature Junctional Complexes	All	not present → present
Junctional Escape Complexes	All	not present → present
Other	All	not present → present
Conduction		
First Degree AV Block	PR > 0.20 s	
2:1 AV Block	All	not present → present
AV Mobitz I	All	not present → present
AV Mobitz II	All	not present → present
Complete Heart Block	All	not present → present
First Degree AV Block	All	not present → present
Incomplete Left Bundle Branch Block	All	not present → present
Incomplete Right Bundle Branch Block	All	not present → present
Intraventricular Conduction Defect	All	not present → present
Left Anterior Hemiblock	All	not present → present
Left bundle-branch block	All	not present → present
Left Posterior Hemiblock	All	not present → present
Prolonged QTc	All	not present → present
Right bundle-branch block	All	not present → present
Wolff-Parkinson-White	All	not present → present
Other	All	not present → present
ST Segment		
Depressed	All	not present → present
Elevated	All	not present → present
Other	All	not present → present
T Waves		
Biphasic	All	not present → present
Flat	All	not present → present
Inverted	All	not present → present
Notched	All	not present → present
Other	All	not present → present
U Waves		
Abnormal	All	not present → present
T-U Fusion	All	not present → present
Other	All	not present → present
Myocardial Infarction		
High Lateral MI 1, AVL	All	not present → present
Septal MI V1, V2, (V3)	All	not present → present
Antero Lateral MI V3-V6	All	not present → present
Inferior MI (2), 3, F	All	not present → present
Extensive Anterior MI 1, L, V1-V6	All	not present → present
Antero Septal MI V1-V4	All	not present → present
Lateral MI 1, L, V5, V6	All	not present → present
Anterior MI V3, V4	All	not present → present
Posterior MI	All	not present → present

Statistical Analysis Plan

Protocol 323-201-00006

Sponsor Provided Criteria for Identifying EC Measurements of Potential Clinical Relevance		
Category	Criterion Value^a	Change Relative to Baseline^a
Diagnosis		
Other	All	not present → present
Morphology		
Left Atrial Abnormality	All	not present → present
Left Ventricular Hypertrophy	All	not present → present
Low Voltage	All	not present → present
Right Atrial Abnormality	All	not present → present
Right Ventricular Hypertrophy	All	not present → present
Brugada Syndrome	All	not present → present
Other	All	not present → present
QT Interval		
Increase in QT	QT > 450 msec (males and females)	
	QT > 480 msec (males and females)	
	QT > 500 msec (males and females)	
Increase in QTcF	QTcF > 450 msec (males and females)	
	QTcF > 480 msec (males and females)	
	QTcF > 500 msec (males and females)	
		Increase of ≥ 30 msec and ≤ 60 msec
		Increase of > 60 msec
Increase in QTcB	QTcB > 450 msec (males and females)	
	QTcB > 480 msec (males and females)	
	QTcB > 500 msec (males and females)	
		Increase of ≥ 30 msec and ≤ 60 msec
		Increase of > 60 msec

^aIn order to be identified as potentially clinically relevant, an on-treatment value must meet the “Criterion Value” OR represent a change from the participant’s baseline value of at least the magnitude shown in the “Change Relative to Baseline” column.

^bNo current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

^cNo current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

Statistical Analysis Plan

Protocol 323-201-00006

Appendix 5 Completer Category Information

Completer Category Information	
Treatment completer; trial completer	• Randomized participant who has taken at least one dose of quabodepistat (OPC-167832), DLM, or BDQ, RHEZ • Does not discontinue treatment in the treatment period (17 weeks for quabodepistat (OPC-167832), DLM, or BDQ /26 weeks for RHEZ) • Has at least some assessments at the 17 week/26 week end-of-treatment visit (completes end-of-treatment visit) • Continues on trial till the end of study visit at 12 months post randomization; completes end of study assessments
Treatment non-completer; trial completer	• Randomized participant who has taken at least one dose of quabodepistat (OPC-167832), DLM, or BDQ, RHEZ • Discontinues treatment prior to the end of the treatment period (17 weeks for OPC-167832, DLM, or BDQ/26 weeks for RHEZ) • Continues on trial till the end of study visit at 12 months post randomization; completes end of study assessments
Treatment completer; trial non-completer	• Randomized participant who has taken at least one dose of quabodepistat (OPC-167832), DLM, or BDQ, RHEZ • Does not discontinue treatment in the treatment period (17 weeks for quabodepistat (OPC-167832), DLM, or BDQ/26 weeks for RHEZ) • Has at least some assessments at the 17 week/26 week end-of-treatment visit (completes end-of-treatment visit) • May or may not continue on trial after end-of treatment visit • Does not continue till the end of study visit at 12 months post randomization; does not complete end of study assessments • Includes participants who do not complete 12 months of post randomization follow-up for any reason: participants who die after end-of-treatment visit; participants lost to follow-up (LTFU) after end-of-treatment visit; participants who withdraw/are withdrawn from the study after end-of-treatment.

Statistical Analysis Plan

Protocol 323-201-00006

Completer Category Information	
Treatment non-completer; trial non-completer	• Randomized participant not treated with quabodepistat (OPC-167832), DLM, or BDQ, RHEZ • OR at least one dose of quabodepistat (OPC-167832), DLM, or BDQ, RHEZ. • If study treatment was started, discontinues treatment prior to the end of the treatment period (17 weeks for quabodepistat (OPC-167832), DLM, or BDQ /26 weeks for RHEZ). • May or may not continue on trial after discontinuing treatment. • If continues on study, discontinues prior to end-of study visit at 12 months post randomization; does not complete end of study assessments at the 12-month timepoint. • Includes participants who: participants who die/are LTFU/withdraw/are withdrawn prior to 17 weeks/26 weeks treatment period, participants who die/are LTFU/withdraw/are withdrawn after discontinuing treatment (prior to 17 weeks/26 weeks) but prior to 12 months post randomization.

BDQ = bedaquiline; DLM = delamanid; LTFU = lost to follow-up; RHEZ = rifampin, isoniazid, ethambutol, pyrazinamide.

Statistical Analysis Plan

Protocol 323-201-00006

Appendix 6 Missing Data for Adverse Events/Concomitant Medications

In general, imputation of partial missing dates will be made for AE onset date, AE resolution date, death date, start and end dates of concomitant therapy, and date of initial diagnosis. Completely missing dates will not be imputed.

In general, if related information on the missing date exists in any other dataset that may help in determining the missing information, it will be used for imputations. Final decisions on key dates may be taken by key members of the study team and must include the study statistician.

Partial AE onset dates will be imputed as follows:

- If only day is missing, it will be set to:
 - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of first dose date.
 - The day of first dose date, if the month/year of the onset of AE is the same as month/year of the first dose date and month/year of the AE resolution date is different.
 - The day of first dose date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose date and month/year of the AE resolution date are same.
- If both day and month are missing, it will be set to the earliest of:
 - January 1 of the year of onset, as long as this date is after the first dose date;
 - Month and day of the first dose date, if this date is the same year that the AE occurred;
 - Last day of the year if the year of the AE onset is prior to the year of the first dose date;
 - AE resolution date.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If missing day only, it will be set to the earlier of (last day of the month of resolution, the day of the date of death if death occurred in that month);
- If missing both day and month, it will be set to the earlier of (December 31 of the year, the day and month of the date of death if death occurred in that year).

For partial start and end dates of concomitant therapies, the AE imputation rules listed above will be applied accordingly.

Statistical Analysis Plan

Protocol 323-201-00006

For partial date of death and date of initial diagnosis, the following rule will be applied:

- If year is missing, no imputation will be made;
- If only year is present, but month and day are missing, June 30th will be used;
- If only day is missing but year and month are present, the 15th of the month will be used.

The above imputations will be modified by the following rules as needed:

- If imputed date for initial diagnosis is $\geq$ study consent date, consent date – 1 will be used;

If the imputed death date is $<$ the last known alive date, later date + 1 will be used.

Statistical Analysis Plan

Protocol 323-201-00006

Appendix 7 SAS Code

Analysis of proportions:

```
proc freq data= datasetname;  
tables treatment * aval / riskdiff (cl=MN) alpha=0.2;  
run;
```

Survival analysis:

```
proc lifetest data=adeft;  
strata hiv cavitation;  
time scctime*censor(1);  
run;
```

Cochran-Armitage trend test:

```
proc freq data= datasetname;  
tables aval * trtn / trend ;  
run;
```

Statistical Analysis Plan

Protocol 323-201-00006

Appendix 8 Determination of 6-month Post End-of-Treatment Favorable/Unfavorable/Not Assessable Outcome

Unfavorable Outcome Criteria	Date to Use	Rationale
1) Clinical progression of pulmonary disease <i>during treatment</i> or the need for an unanticipated surgical intervention for TB (e.g., lobectomy). <i>Progression of Pulmonary Disease</i>	Stop date of IMP	If participant has clinical progression while on IMP, investigators would stop the IMP and start the participant with rescue meds.
2) Any growth of M tuberculosis from an extrapulmonary site during the post-treatment period (Note: excludes reinfection with a new strain of M tuberculosis). <i>Growth of M Tuberculosis</i>	AE start date Check for terms provided for extrapulmonary AEs	If participant developed TB from extrapulmonary site, this would be reported as AE and the start date would be the date of sample collection that confirmed positive for MTb.
3) Signs and symptoms of active tuberculosis during the follow-up period (i.e., after the end of treatment), including radiographic worsening compared to baseline findings, resulting in re-initiation of anti-mycobacterial therapy (Note: excludes a re-initiation that is subsequently found to be due to a misdiagnosis and/or alternative diagnosis). <i>Signs and Symptoms of Tuberculosis</i>	Start Date of Rescue Meds	Rescue Medication criteria 3: "If, in the opinion of the investigator, a participant is clinically deteriorating, based on any combination of signs, symptoms, or chest radiograph data. Participants in Arm 4 will be managed according to local guidelines if not responding to therapy." Start date of rescue medication: This confirms PI decision of unfavorable outcome due to clinical progression during post treatment period.
4) Death during treatment or follow-up <i>Death During Treatment or Follow-up</i>	Date of Death	Date of death reflects time of event that is death.
5) A sputum culture with growth of M tuberculosis at certain time points as follows: a) Failure to achieve SCC by the end of the treatment period that results in a change in anti-mycobacterial therapy; <i>Failure to Achieve SCC</i> b) Microbiologic relapse during the follow-up period (i.e., after the end of treatment) (Note: excludes reinfection and requires more than 1 positive sputum culture with a new strain of M tuberculosis). <i>Microbiologic Relapse During Follow-up</i>	a) Date of sputum collection at end of treatment; b) Date of first relapse (regular mgit) from the genotyping data	a) Date of sputum collection at Week 17 or Week 26 that confirms participant is still positive for MTb, hence decision to start rescue meds; b) Date of first relapse (based on regular mgit only) as collected in the genotyping CRF page

Statistical Analysis Plan

Protocol 323-201-00006

AE = adverse event; CRF = case report form ; IMP = investigational medicinal product; TB = tuberculosis; mgit = Mycobacteria Growth Indicator Tube®; MTb = Mycobacterium tuberculosis; SCC = sputum culture conversion.

For each criterion, an unfavorable outcome is indicated by a date for the occurrence of that criterion prior to the 6-months post-end-of-treatment date. The overall unfavorable outcomes 6-months post-end-of-treatment occurs at the earliest of the dates identified in above table. If all dates are missing, then the participant has a favorable outcome 6-months post-end-of-treatment.

If a participant does not have sputum culture assessments at Weeks 34 and 39, he will be considered as “Not assessable” for the 6-months-post-end-of-treatment favorable outcome.



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