

ACTG A5343

A Trial of the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, among Participants Taking Multidrug Treatment for Drug-Resistant Pulmonary Tuberculosis

ClinicalTrials.gov Identifier: NCT02583048

Primary Statistical Analysis Plan

Version 1.0

July 11, 2018

This is ACTG A5343 SAP Version 1.0 with names of authors, names of publication writing team members and analysis timeline redacted.

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1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcomes measures of ACTG A5343 that will be included in the primary manuscript, and which address the primary and key secondary objectives of the study; the pharmacology objectives will be addressed separately. The Primary SAP outlines the general statistical approaches that will be used in the analysis. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the primary statistical analysis report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov. Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Statistical Analysis Report are included in the Analysis Implementation Plan (AIP).

A separate Statistical Analysis Plan for Other Objectives and Outcome Measures will be developed once results for the Primary and key Secondary Objectives are known, and analyses will be presented in a separate report. These analyses may include nonlinear mixed-effects modeling of drug concentrations.

Data for the Primary Analysis Report will be downloaded when Week 24 ECG data are available for the last enrolled participant, all queries have been resolved, and the database is frozen for analysis.

The Primary Analysis Report will be used for submission of results to ClinicalTrials.gov. Results for primary outcomes are required to be submitted within one year of the primary completion date (PCD), which is the date the last participant is examined for the purposes of data collection for the primary outcome measure. For this study, the PCD is based on ECG data collected at the week 24 visit. Results for secondary outcome measures are due one year after the last participant reaches Week 28.

1.2 Key updates to the SAP

Version	Date	Content/changes
1.0	July 11, 2018	Original version of SAP.

2 Protocol Overview

2.1 Study design

ACTG A5343 is a phase II, randomized, open-label, three-arm pharmacokinetic (PK) and safety trial of the anti-tuberculosis drugs bedaquiline (BDQ) and delamanid (DLM) in participants with pulmonary infection with multidrug-resistant *M. tuberculosis* (MDR-TB). Participants will be randomized to one of three arms. Participants in arms 1, 2, and 3 will receive BDQ, DLM, or both drugs in combination, respectively, for 24 weeks together with multidrug background treatment (MBT) for MDR-TB.

The study will enroll a total of 84 evaluable men and women age 18 or older (28 per arm), with pulmonary MDR-TB, with or without HIV co-infection. Randomization will be stratified by HIV status, with institutional balancing. Participants will be followed for a total of 128 weeks: 24 weeks on study treatment, followed by 104 weeks of follow-up.

To be eligible to enroll in the study, participants must have documented pulmonary infection due to strains of *M. tuberculosis* from a sputum sample collected within 60 days prior to entry with resistance to isoniazid (INH) and rifampin (RIF) and susceptibility to fluoroquinolones and aminoglycosides; resistance and susceptibility may be determined by either genotypic or phenotypic testing. Participants with HIV-1 infection may enter the study provided their CD4+ count is ≥ 100 cells/mm³ within 60 days prior to entry. In addition to study TB drugs, participants will need to take MBT for MDR-TB for a minimum of 7 days within the 10 days prior to entry. Previous treatment for MDR-TB (other than for the qualifying episode) or receipt of BDQ or DLM at any time in the past is exclusionary. In addition, QTcF interval greater than 450 ms within 72 hours prior to entry, clinically significant ECG abnormalities, current clinically relevant cardiovascular disorder, known family history of Long QT Syndrome, and several other cardiovascular-related criteria are exclusionary (see Protocol section 4.2).

Version 1.0 of the protocol stated that study participants were to be hospitalized per standard of care for initiation of MDR-TB treatment for at least the first two months after randomization and possibly longer than two months if they were too ill for discharge.

Based on an interim monitoring review added to version 3.0 of the protocol, to potentially allow the duration of the initial hospitalization to be shortened, the Tuberculosis Transformative Science Group (TB TSG) Study Monitoring Committee (SMC) recommended that participants be offered a 2-week hospitalization period and that 8 weeks of hospitalization was no longer required. LOA #1 to Protocol version 3.0 clarified and codified this protocol change. (See Protocol History, below).

This is a limited-site study open to 3 non-US sites: TASK (Bellville, South Africa), SATVI (Capetown, South Africa) and Barranco (Lima, Peru).

2.1.1 Study treatment: Study TB drugs

Participants will be randomized to one of three arms:

- Arm 1: BDQ 400 mg PO QD for 2 weeks followed by 200 mg PO TIW for 22 weeks
- Arm 2: DLM 100 mg PO BID for 24 weeks
- Arm 3: Both BDQ and DLM (same doses and durations as in Arms 1 and 2, respectively)

Participants will have 185 days from enrollment to complete 168 days (24 weeks) of TB study drug. (The extra seventeen days are allowed for the possibility of missed TB study drug during the 24 week period.)

2.1.2 Study treatment: Study Antiretroviral Therapy (ART):

Participants with HIV infection can participate provided they are taking an acceptable ART regimen. For those participants without contraindications, study dolutegravir (DTG) at a dose of 50 mg once daily will be offered, to be used in combination with two NRTIs until study completion (week 128). The other acceptable ART regimen is nevirapine (NVP) plus two NRTIs. NRTIs are provided by the local program. PIs and EFV are contraindicated though switching from a regimen containing these to an acceptable study ART regimen prior to starting study TB drugs is allowed (as per protocol section 5.4).

For participants who are HIV treatment naïve, it is recommended that DTG (study ART) plus two NRTIs be started approximately 2 weeks following initiation of study TB drugs. For participants already on ART with EFV or a boosted PI at the time of screening, or who require a switch from the previous ART for another reason, it is recommended that DTG-based ART be started the day following discontinuation of their previous regimen. Per Letter of Amendment #2 for protocol version 3.0, HIV-positive female participants of reproductive potential, are required to use contraceptive for the full duration of time the participant is taking DTG (ie, through study completion at week 128). (See Protocol History below.)

2.1.3 Multidrug Background Treatment (MBT):

While receiving study TB drugs, participants will also receive MBT for MDR-TB that includes at least 3 drugs to which the organism is thought or known to be susceptible (as per protocol section 5.4). In many participants this will be a standardized, locally-available regimen, but individualization of regimens based on available culture and susceptibility data, or treatment history, may be needed. Participants should take MBT for all 128 weeks on study.

2.1.4 Evaluations

ECGs will be performed (in triplicate, 5-10 minutes apart) at entry; every two weeks during administration of BDQ and/or DLM (even-numbered weeks 2-24); and at week 28 (4 weeks after TB study drug(s) have been discontinued). To minimize variability in QT intervals, ECG trace data are automatically transmitted to the central ECG laboratory (Quintiles) for determination of QT interval and other ECG measures.

Intensive PK sampling will be performed at weeks 2, 8, and 24. Sparse PK sampling will be performed during study treatment at weeks 4, 6, 10, 12, 14, 16, 18, 20 and 22, and at week 28 (4 weeks after study TB drugs have been discontinued). Assays will be performed for DLM and its DM-6705 metabolite, and for BDQ and its M2 metabolite.

Hair collection will be performed for measurement of DLM, BDQ, and MBT drugs over the course of the study to assess long-term drug exposures.

In HIV-1 positive participants, viral load will be measured at the time points indicated in protocol section 6.0.

Other clinical and laboratory evaluations (e.g. signs/symptoms, diagnoses, chemistry, hematology, sputum smears, adherence) will also take place on a regular basis through week 28 and then approximately quarterly through week 128 as defined in protocol section 6.0.

2.1.5 Replacements

Because BDQ and DLM are known to have long half-lives, there is no plan to replace participants or reschedule PK visits for participants who miss the prior two doses of BDQ or DLM or who do not eat the standardized meals on the intensive PK days.

2.1.6 Permanent and Premature Treatment Discontinuation Criteria (protocol section 8.1)

- Failure by the participant to attend 3 consecutive study visits.
- Protocol-defined drug-related toxicity (see protocol section 7.0 Toxicity).
- Requirement for prohibited concomitant medications (see protocol section 5.4.2)
- Pregnancy or breastfeeding.
- Request by participant to terminate treatment.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

2.1.7 Premature Study Discontinuation Criteria (protocol section 8.2)

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the IRB/Ethics Committee, Food and Drug Administration (FDA), NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

These participants will not be replaced.

2.1.8 Duration of study and anticipated time to meet accrual target

The duration of the study is 128 weeks from entry through the final clinic visit.

Originally the study was expected to enroll about 8-10 participants per month across at least two ACTG sites, and to meet the accrual target of 84 participants in less than 12 months.

2.1.9 Sample size considerations

Sample size calculations were chosen to provide specific precision of 95% confidence intervals (CIs around (1) arm-specific QTcF interval changes from baseline, and (2) between-arm differences in

changes from baseline (BDQ+DLM arm vs. BDQ-alone arm, and BDQ+DLM arm vs. DLM-alone arm). With 25 evaluable participants per arm with complete ECG data, the anticipated precision these CIs are (1) ± 4.5 milliseconds (ms) and (2) ± 6.0 (ms), respectively.

Letter of Amendment #2 to Protocol version 3.0 was released on 06/04/2018, called for interim calculation of 99.9% CIs for the primary outcome measures. To account for the interim CIs, the LoA specified that coverage probabilities of CIs in the final analysis will be adjusted to 95.1%. (A participant who is in the analysis population is consider evaluable.)

2.2 Protocol History

The study opened under version 1.0 of the protocol, dated 07/13/2015.

Clarification Memo #1, dated 08/25/2015: Corrected an inconsistency in the recommended time frame for switching ART treatment from EFV-based treatment to DTG-based treatment among participants with HIV co-infection. The 3-day window between starting DTG and starting study TB drugs was modified to a 7-day window to allow the needed days for EFV to wash out.

Letter of Amendment #1, dated 06/20/2016: Updated the Expedited Adverse Event (EAE) Reporting Requirements for A5343 adding several additional AEs that must be reported in an expedited manner.

Protocol version 2.0 was released on 12/23/2016: Its main purpose was to add two exploratory objectives to the study, add screening viral load testing and genotyping for HIV-infected participants who have been on ART for 6 months or longer, and clarify the management of participants who prematurely discontinue study treatment. This version incorporates all prior changes from Letter of Amendment #1 and Clarification Memo #1. In addition, minor changes were made in the protocol document for clarification purposes.

A Letter of Amendment #1 to Protocol version 2.0, dated 03/14/2017, clarified the directly observed therapy requirements for those on the BDQ arm and added Grade 4 events to the list of adverse events that must be reported in an expedited manner.

A5343 protocol version 3.0 was released on 07/18/2017. The main amendments were: (1) a change to inclusion criteria to allow individuals with rifampin mono-resistant TB (RR-TB) to enter the study, and (2) introduction of a new interim monitoring trigger and review, to potentially allow the duration of the initial hospitalization to be shortened.

A Letter of Amendment #1 to Protocol version 3.0 was released on 11/20/2017. Per A5343, Version 3.0, an interim review was planned after QTcF data through week 8 were available for at least 12 participants on the BDQ+DLM regimen (study arm 3), to help determine if it is safe to decrease the duration of hospitalization from 8 weeks to 2 weeks. The TB TSG SMC reviewed the interim report on these data. Based on the report, they recommended that participants be offered a 2-week hospitalization period, and that the 8 weeks of hospitalization no longer be required. The main purpose of LOA #1 to Protocol

version 3.0 was to clarify that the required hospitalization stay had been reduced from 8 weeks to 2 weeks.

A Letter of Amendment #2 to Protocol version 3.0 was released on 06/04/2018 in response to the release of a safety announcement on 05/18/2018 by The World Health Organization (WHO), the U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA) regarding an unplanned analysis of an ongoing study in Botswana of pregnant HIV-positive women on antiretroviral therapy. In that analysis, investigators noted an increase in neural tube defects in infants born to women who conceived while on DTG. This prompted regulatory agencies and the WHO to issue advice to health care professionals and HIV-positive patients that include avoiding DTG in HIV-positive women who are contemplating pregnancy, testing for pregnancy prior to starting DTG, and ensuring adequate birth control use among women taking DTG. Based on discussions within the US Division of AIDS (DAIDS) and regulatory groups, changes to the A5343 study were needed to revise the pregnancy/contraception language for HIV-infected women of reproductive potential who receive DTG.

The main purpose of this LOA was thus to update the pregnancy/contraception requirements and DTG risk information in the protocol and the sample informed consent form, and to add this interim analysis to evaluate precision on primary outcome estimates and to conduct an early look at safety and QT intervals in the setting of slow enrollment given the global need for such information.

A5343 protocol version 4.0 was released on 06/26/2018. The main purpose of this amendment was to add an assessment of cerebrospinal fluid (CSF) concentrations of DLM and BDQ for up to 16 participants with MDR-TB or RR-TB enrolled in A5343, via an optional lumbar puncture to be performed at week 8 or week 24. The amendment also incorporates all prior changes from the version 3.0 Letter of Amendment (LOA) #1 (11/20/17) and LOA #2 (06/04/18).

2.3 Hypotheses

2.3.1 Primary hypothesis

Co-administration of delamanid (DLM) and bedaquiline (BDQ) (with multidrug background treatment [MBT] for multidrug resistant TB infection [MDR-TB] or rifampin-mono-resistant TB [RR-TB]) will increase the duration of the QT interval (QTcF, as measured on electrocardiogram (ECG), adjusted for heart rate using the Fridericia correction formula) compared to administration of either drug alone (with MBT), but the combined effects on the QT interval will be no greater than additive.

2.3.2 Secondary Hypotheses

- 2.3.2.1 When DLM and BDQ are co-administered with MBT for TB infection, clinically significant QTcF prolongation (see section 7.1.1 for definition) will be uncommon.

2.3.2.2 Co-administration of BDQ and DLM (in the context of MBT) for MDR-TB or RR-TB will not significantly affect concentrations (area under the concentration-time curve, or AUC) of either drug (or their main metabolites, M2 and DM-6705, respectively).

2.4 Study objectives and outcome measures

2.4.1 Primary Objectives

2.4.1.1 To estimate the mean changes from baseline (averaged over weeks 8-24) in QTcF when DLM and BDQ are co-administered (along with MBT; Arm 3), when BDQ is administered without DLM (along with MBT; Arm 1) and when DLM is administered without BDQ (along with MBT; Arm 2).

2.4.1.2 To compare the mean change from baseline (averaged over weeks 8-24) in QTcF when BDQ and DLM are co-administered (with MBT) to the mean change observed when each drug is administered alone (with MBT) (separate comparisons of Arm 3 to Arm 1 and Arm 3 to Arm 2).

Outcome measure. For both primary objectives, the outcome measure is participant-specific changes from baseline in QTcF among the participants on each arm. QTcF measurements from the week 0 visit contribute to estimation of baseline QTcF, and QTcF measurements from weeks 8 through 24 contribute to estimation of the on-treatment QTcF. QTcF replicates arise from 3 separate complexes, ideally measured 5-10 minutes apart during the study visit. If fewer than 3 values are available, the 1 or 2 available QTcF values are used. See Analysis Population below for details of which QT intervals will be used in the primary and secondary analyses of QT intervals.

2.4.2 Secondary Objectives

2.4.2.1 To estimate the proportion of participants who exhibit QTcF >500 ms at any time during study treatment, by arm.

Outcome measure: The participant-specific outcome measure is the visit-specific average of the 1-3 available QTcF values.

2.4.2.2 To estimate the proportion of participants who exhibit an increase from baseline in QTcF of greater than 60 ms at any time during study treatment, by arm.

Outcome measure: The participant-specific outcome measure is the visit-specific average of the 1-3 available QTcF values.

2.4.2.3 To describe visit-specific QTcF changes from baseline while on study drug treatment and following completion of study treatment (at week 28), for participants in Arm 1 (BDQ), Arm 2 (DLM), and Arm 3 (BDQ and DLM).

Outcome measure: The participant-specific outcome measure is the average of the 1-3 QTcF values available from the week 28 visit.

2.4.2.4 To estimate, by arm, the proportion of participants for whom the following occurs: (a) absolute QTcF >480 and ≤500 ms and (b) (separate measure) QTcF increase from baseline of >30 and ≤60 ms.

Outcome measure: The participant-specific outcome measure is the visit-specific average of the 1-3 available QTcF values.

2.4.2.5 To compare the pharmacokinetics (PK) of BDQ when given together with DLM with MBT for MDR-TB or RR-TB (Arm 3) versus when given alone with MBR for MDR-TB or RR-TB (Arm 1).

Outcome measure: Outcome measures are participant-specific PK parameters for BDQ and its M2 metabolite, estimated using noncompartmental methods applied to concentrations from intensive PK sampling visits (weeks 2, 8, and 24). PK parameters consist of C_{min} ; C_{max} ; and area under the concentration time curve pre-dose to 22 hours (AUC_{0-22h})¹. Weeks 2, 8, and 24 PK parameters will be summarized separately. This outcome measure is limited to the analysis population in arms 1 and 3. If PK sampling occurs on days when BDQ dose is not taken (ie, if relative time post dose is >25 hours), non-model-based PK parameters will not be calculated, although model-based secondary/exploratory model-based analyses will include the concentrations.

2.4.2.6 To compare the PK of DLM when given together with BDQ with MBT for MDR-TB or RR-TB (Arm 3) versus when given alone (Arm 2).

Outcome measure: Outcome measures are participant-specific PK parameters for DLM and its DM6705 metabolite, estimated using noncompartmental methods applied to concentrations from intensive PK sampling visits (weeks 2, 8, and 24). PK parameters consist of C_{min} ; C_{max} ; and area under the concentration time curve from pre-dose to 11 hours (AUC_{0-11h})². Week 2, 8, and 24 PK parameters will be summarized separately. This outcome measure is limited to the analysis population in arms 2 and 3.

2.4.2.7 To describe the safety and tolerability of study treatment, by arm.

Outcome measure: Outcome measures are: (1) occurrence of Grade 3 or higher adverse event of any type at any time through week 24 (safety), (2) occurrence of death at any time while on study TB drug (safety), (3) discontinuation of study TB drug(s) for any reason prior to week 24. Analysis is conducted on the safety population.

¹ The necessity of separating BDQ and DLM dosing by one hour leads to the last sample for BDQ assay being collected at 22h rather than the more standard 24h.

² The necessity of separating BDQ and DLM dosing by one hour leads to the last sample for DLM assay being collected at 11h rather than the more standard 12h.

3 Definitions

3.1 Baseline

Baseline (study entry, week 0) is defined as the date on which the participant initiated study TB drug(s). Values used for baseline (Week 0) will be the latest evaluation on or before this date.

3.2 Analysis population

A participant is considered to have complete ECG data if 3 ECGs were collected at single baseline visit and at each of the 9 on-study-TB-drug visits, provided the participant is still taking study TB drug(s) at the time of the visit; see details below.

A participant is in the analysis population through the week 24 visit provided there were no interruptions in dosing of study TB drug(s). Details:

- If a participant discontinues study TB drug permanently prior to week 24 due to Grade 3 or higher prolongation in QT interval (as defined in Section 7.1 of the protocol), the QTcF value from the participant's last visit will be carried forward to subsequent weeks (under the assumption that if the participant had continued study TB drug(s), the QT prolongation would likely have persisted or increased).
- If a participant discontinues study drug permanently prior to week 24 for a reason other than Grade 3 or higher prolongation in QT interval, available QTcF values obtained while taking study TB drug will be included but will not be carried forward. (The participant is removed from the analysis population as of the date after the last dose of study TB drug(s).)
- For temporary discontinuations of study TB drug: (a) If the discontinuation lasts for 7 or fewer days, the ECG at the next scheduled visit will be performed and the QTcF value from that visit will be used in the analysis. (b) If the discontinuation lasts for 8-14 days, the ECG at the next scheduled visit will be performed and the QTcF value from that visit will be treated as missing. The preceding text is taken directly from the protocol, but is difficult to interpret. As a clarification: For temporary discontinuations of study TB drug: At any one visit at which ECG is measured during a temporary period of without doses, if the participant has taken a dose within 7 days of the visit, the QTcF value will be used in analysis. If it has been more than 7 days since the last dose, the QTcF value will not be used in analysis.

3.3 Safety population

The safety population consists of participants who take at least one dose of study TB drug(s).

3.4 QT intervals

The QT interval is the duration of time (in milliseconds, ms) between the Q and T waves in the heart's electrical cycle. The outcome measure, QTcF, is the duration of the QT interval corrected for heart rate using the Fridericia correction formula.

4 Statistical methods

4.1 General considerations

Baseline characteristics will be summarized by arm, but there will be no statistical comparisons comparing arms because of the randomized study design.

Inference consists of point estimates and confidence intervals (CIs). With the exception of an adjustment described in the Letter of Amendment #2 to Protocol version 3.0, CI coverage will not be adjusted for multiple intervals. For the interim analysis described in CIs in the Letter of Amendment #2 to Protocol version 3.0, CIs will be constructed to have 99.9% coverage. To maintain no less than 95% simultaneous coverage for both the interim and final analysis, CIs reported in the final analyses will have 95.1% coverage.

Categorical data will be summarized using N (%), and continuous data using N, min, Q1, median, Q3, max, and mean (standard deviation [SD]) (when appropriate). Any modifications to outcome measures after the team has seen data that were collected after entry will be identified as such in the analysis report.

4.2 Visit schedule and analysis windows

ECGs for determination of QT interval duration are conducted at study entry and at weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 and 28. Intensive PK sampling I plasma for BDQ and DLM is conducted on at weeks 2, 8 and 24. For weeks 2-8, the visit window is ± 3 days; for weeks 10-24, the visit window is ± 7 days; for week 28, the visit window is ± 2 week.

For the purposes of analysis, visit windows will be formed around each study visit using the midpoints between adjacent weeks as cutoffs, and potentially including assessments collected outside the recommended visit windows described above. If there are multiple evaluations within the analysis window for a given visit, the evaluation closest to the scheduled study week will be used, and the earlier measurement will be used if there are two measurements which are equally distant from the scheduled week.

4.3 Analyses of outcomes measures

4.3.1 Primary QT prolongation outcomes

A mixed-effects ANOVA model, with fixed effects for arm and period (baseline vs. on-treatment) and random effects for participant, will be fit to data from participants on all arms, with handling of QTcF values as described in **Section 3.2**.

Objective 2.4.1.1. For the primary analysis, the QT prolongation (change from baseline) on Arm 3 will be represented as the estimated contrast between periods, along with the corresponding model-based 95.1% CI. QT prolongations on Arms 1 and 2 will be similarly estimated. (CIs with 99.9% coverage are used in the July 2018 interim analysis.)

Objective 2.4.1.2. For the primary analysis, the difference between QT prolongations on Arms 3 and 1 will be estimated as the corresponding contrast (Arm 3 change from baseline minus Arm 1 change from baseline) along with the corresponding model-based 95.1% CI. Arms 2 and 3 will be similarly compared. (CIs with 99.9% coverage are used in the July 2018 interim analysis.)

4.3.2 Secondary QT prolongation outcomes

Objectives 2.4.2.1, 2.4.2.2, and 2.4.2.4. The analysis will be conducted in the safety population. (Because the study TB drugs have a long half-life, participants will be included in the proportion whether or not they took study TB drug(s) through the corresponding visit week.) For each binary outcome listed under **Objectives 2.4.2.1, 2.4.2.2, and 2.4.2.4**, numbers and proportions of participants experiencing one or more such event will be summarized by arm, along with 95% exact Clopper-Pearson binomial CIs. Between-arm comparisons will not be conducted.

Objective 2.4.2.3. Arm- and visit-specific within-participant changes from baseline in QTcF will be described, beginning with the first on-treatment ECG in the Schedule of Events, and continuing through the last ECG measured after scheduled discontinuation of study TB drug(s) at week 28. Descriptions will include N, minimum, Q1, median, Q3, maximum, mean and standard deviation (SD). For participants who discontinue study TB drug(s) prematurely, QTcF changes will be excluded from analysis; however, in a sensitivity analysis, QTcF changes from such participants will be carried forward as described in **Section 3.2**. To allow a visual comparison of arms with respect to time effects, medians and IQRs in changes from baseline will be plotted against week on a single graph but with separate lines (colors, symbols) for each arm. In a separate graph, week-specific mean changes and associated 95% CIs will be plotted against week. Between-arm comparisons will not be conducted.

4.3.3 Secondary safety and tolerability outcomes

Objective 2.4.2.7. The analysis will be conducted in the safety population. For the binary outcomes listed under **Objective 2.4.2.7**, numbers and proportions of participants experiencing one or more such event will be summarized by arm, along with 95% exact Clopper-Pearson binomial CIs.

4.3.4 PK outcomes

Objectives 2.4.2.5 and 2.4.2.6. For BDQ and its M2 metabolite, and for DLM and its DM-6705 metabolite: Participant-specific PK parameters C_{min} , C_{max} and AUC will be summarized by arm and week (weeks 2, 8, and 24). Effects of DLM co-administration on BDQ PK parameters will be summarized by estimation of (week-specific) geometric mean ratios (GMRs), BDQ PK parameter with relative to without DLM co-administration. Effects of BDQ co-administration on DLM PK parameters will be summarized by estimation of GMRs, DLM PK parameter with relative to without BDQ coadministration. CIs around the GMRs will be constructed to have 90% coverage. (Nonlinear mixed-effects modeling of the PK of BDQ and DLM will be conducted; this analysis is outside the scope of this SAP.)

5 Report components

Detailed descriptions of the content of each of the following sections are given in the AIP.

-
1. Study entry
 - a. Screening
 - b. Enrollment
 - c. Eligibility errors
 2. Baseline characteristics
 3. Protocol deviations
 4. Study status
 5. Study treatment status (study TB drug(s))
 6. Changes/interruptions to study TB drug(s) during study follow-up
 7. QT prolongation
 8. Other safety:
 - a. ECG findings other than QT intervals
 - b. Signs/symptoms, labs, diagnoses
 - c. Pregnancies
 - d. Deaths
 9. BDQ and DLM PK parameters