Statistical Analysis Plan Amendment 4

Study ID: 214912

Official Title of Study: A parallel group, Phase 2A, randomised, open label treatment study to assess the early bactericidal activity, safety and tolerability of GSK3036656 administered as a two drug combination with novel and established antitubercular agents, or standard of care in adults with rifampicin-susceptible pulmonary tuberculosis.

NCT number: NCT05382312

Date of Document: 18-June-2025

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A parallel group, Phase 2A, randomised, open label treatment study to assess the early bactericidal activity, safety and tolerability of GSK3036656 administered as a two drug combination with novel and established antitubercular agents, or standard of care in adults with rifampicin-susceptible pulmonary tuberculosis.

Study Number: 214912

Compound Number: GSK3036656

Abbreviated Title: Early bactericidal activity, safety & tolerability of oral GSK3036656 in a dual combination with novel and established antitubercular agents, or standard of care in adults with rifampicin susceptible pulmonary tuberculosis.

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**

Copyright 2025 the GSK group of companies or its licensor. All rights reserved.
Unauthorised copying or use of this information is prohibited.

TABLE OF CONTENTS

PAGE

TITLE PAGE 1

VERSION HISTORY 4

1. INTRODUCTION 8
   - 1.1. Objectives, Estimands and Endpoints 8
     - 1.1.1. Estimand for Primary Endpoint 9
     - 1.1.2. Estimands for Secondary Endpoints 10
   - 1.2. Study Design 11

2. STATISTICAL HYPOTHESES 13
   - 2.1. Multiplicity Adjustment 14

3. ANALYSIS SETS 14

4. STATISTICAL ANALYSES 14
   - 4.1. General Considerations 14
     - 4.1.1. General Methodology 14
     - 4.1.2. Baseline Definition 15
   - 4.2. Primary Endpoint Analyses 15
     - 4.2.1. Definition of endpoint/estimand 15
     - 4.2.2. Main analytical approach 15
     - 4.2.3. Additional Summaries and Figures 16
   - 4.3. Secondary Endpoints Analyses 17
     - 4.3.1. Secondary EBA Endpoints 17
     - 4.3.2. Secondary Safety Endpoints 17
   - CCI [redacted] 18
   - 18
   - 18
   - 4.5. Safety Analyses 20
     - 4.5.1. Extent of Exposure 20
     - 4.5.2. Adverse Events 20
     - 4.5.3. Additional Safety Assessments 21
   - 4.6. Other Analyses 22
     - 4.6.1. Subgroup analyses 22
     - 4.6.2. Other variables and/or parameters 23
   - 4.7. Interim Analyses 23
   - 4.8. Changes to Protocol Defined Analyses 24

5. SAMPLE SIZE DETERMINATION 24
   - 5.1. Sample Size Sensitivity 25

6. SUPPORTING DOCUMENTATION 26
   - 6.1. Appendix 1 Study Population Analyses 26
     - 6.1.1. Participant Disposition 26
     - 6.1.2. Demographic and Baseline Characteristics 26
     - 6.1.3. Protocol Deviations 26
     - 6.1.4. Prior and Concomitant Medications 26
   - 6.2. Appendix 2 Data Derivations Rule 28

6.2.1. Criteria for Potential Clinical Importance 28
6.2.2. Study Period 29
6.2.3. Study Day and Reference Dates 29
6.2.4. Assessment Window 29
6.2.5. Multiple measurements at One Analysis Time Point 30
6.2.6. Handling of Partial Dates 30

7. REFERENCES 33

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP 1.0	08 Apr 2022	Protocol (14-Dec-2021)	Not Applicable	Original version
SAP 2.0	30 Jan 2024	Protocol Amendment 3 (17-Aug-2023)	Addition of treatment arms and Interim analyses	Updated as per changes made in protocol amendments 2 and 3
SAP 3.0	18 Jun 2025	Protocol Amendment 4 (18-Jun-2024)	Included additional information related to analysis of Microsampling concentration	Updated to get the Blood to Plasma corrected microsampling concentration
SAP 4.0	18 Jun 2025	Protocol Amendment 4 (18-Jun-2024)	Removal of the sensitivity analysis and other minor updates including:	Emerging data for ganfeborole suggests that the change in log_{10}CFU from baseline to Day 14 does not follow a bilinear pattern. As a result, the sensitivity analysis section has been removed.
			Removal of the COVID-19 Assessment and COVID 19 AEs	Displays relating to COVID-19 are no longer required.
			Scheduled vital signs assessments at	Taking the average of all 3 datapoints uses

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			screening have no time recorded. For subjects who have 2 additional unscheduled readings with time recorded, the average of the 3 readings will be calculated. This is done without confirmation that the unscheduled readings occurred at least 1 minute but no more than 5 minutes apart from the planned reading as required by the protocol. Additional text has been added in section 6.2.5 to document this.	all available information.
			The definition of the Efficacy analysis set has been amended to account for participants administered the wrong treatment for the duration of the trial.	Given this is a Ph2a study where it is important to understand the bactericidal activity of each dual combination, participants will be analysed according to the

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				treatment they received.
			Section 4.3.1: The following text has been added: “Due to the skewed distribution of the TTP results, values will be log-transformed prior to summarising and analysis, i.e.log_{10}TTP will be the response variable. log_{10}TTP replaces TTP in sections 4.3.1.2 and 4.3.1.4.	TTP data is positively skewed and log_{10}TTP is used in the summaries and analysis.
			Section 4.5.3.1: Microalbumin has been deleted from the list of urinalysis parameters. Section 4.5.3.3: RR interval and QRS axis have been deleted from the list of parameters.	Microalbumin has not been collected RR interval and QRS axis have not been collected.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 6.1.2: smoking status and treatment history have been included. Some references have been removed from Section 7.	These variables were omitted in error. Section 7 had included references that had not been cited in the document.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 214912. Details of the planned final analyses are provided.

Additional details with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To estimate the early bactericidal activity of GSK3036656 in combination with either delamanid, bedaquiline, BTZ-043, pretomanid, moxifloxacin or linezolid, and oral delamanid in combination with oral bedaquiline over 14 days of once daily repeat dosing, as measured by the number of colony forming units (CFU).	• Change in log_{10}CFU from baseline to Day 14 (EBA CFU_{0-14}).
Secondary	
• To estimate the early bactericidal activity of GSK3036656 in combination with either delamanid, bedaquiline, BTZ-043, pretomanid, moxifloxacin or linezolid, and oral delamanid in combination with oral bedaquiline over 14 days of once daily repeat dosing, as measured by time to sputum culture positivity (TTP).	• Change in TTP[1] from baseline to Day 14 (EBA TTP_{0-14}).
• To assess the safety & tolerability of GSK3036656 administered once daily in combination with either delamanid, bedaquiline, BTZ-043, pretomanid, moxifloxacin or linezolid over 14 days to participants with pulmonary tuberculosis.	• Incidence of serious adverse events and adverse events of grade 3 severity or higher. • Incidence of adverse events considered by the investigator to be possibly, probably or definitely related to study drug. • Incidence of participants withdrawn from the treatment/study due to adverse events. • Incidence of electrocardiogram (ECG) values of potential clinical importance (PCI). • Incidence of clinical chemistry laboratory values of PCI. • Incidence of haematology laboratory values of PCI. • Incidence of vital signs parameters of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) of PCI.

Objectives	Endpoints
CCI	[redacted]

1 Time to sputum-culture positivity is the time between sample inoculation and detection of mycobacterial growth.

1.1.1. Estimand for Primary Endpoint

The primary clinical question of interest is: What is the treatment effect on the early bactericidal activity (EBA) after 14 days of treatment with either GSK3036656+bedaquiline, GSK3036656+delamanid, GSK3036656+BTZ-043, GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin or bedaquiline+delamanid, in participants with drug sensitive (rifampicin-susceptible) pulmonary tuberculosis, had participants completed the 14 days of treatment and no rescue therapy had been available?

The estimand is described by the following attributes
[ICH Harmonized Guideline, 2019]:

- Population: participants with a new, untreated episode of drug sensitive (rifampicin-susceptible) pulmonary tuberculosis.
- Treatment condition: GSK3036656+bedaquiline, GSK3036656+delamanid, GSK3036656+BTZ-043, GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin, bedaquiline+delamanid, or standard of care (SoC) given daily for 14 days.
- Variable/endpoint: Change from baseline to day 14 in log_{10}CFU (EBA CFU_{0-14}).
- Summary measure: Mean change from baseline.
- Intercurrent events:
  - Study treatment discontinuation – hypothetical strategy
  - Use of rescue medication - hypothetical strategy
- Rationale for estimand: Clinical interest lies in estimating the direct effect of randomised treatment on bactericidal activity over 14 days, an indicator of clinical efficacy. The hypothetical strategy is motivated by the potential confounding of EBA data after using rescue medication, or stopping randomised treatment. Only data up to the time of treatment discontinuation/rescue will be included in the analysis.

1.1.2. Estimands for Secondary Endpoints

- **Secondary EBA Estimand**

For the secondary endpoint of change from baseline to day 14 in time to sputum culture positivity (EBA TTP), the estimand will follow a similar approach to the primary estimand for the primary endpoint (Section 1.1.1) and will use the same strategies for the intercurrent events.

- **Safety Estimands**

The primary question of interest with regards safety is: What is the safety profile of 14 days of treatment with either GSK3036656+bedaquiline, GSK3036656+delamanid, GSK3036656+BTZ-043, GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin or bedaquiline+delamanid, in participants with drug sensitive (rifampicin-susceptible) pulmonary tuberculosis, regardless of study treatment discontinuation or the initiation of rescue therapy?

For each of the secondary safety endpoints, the estimand is described by the following attributes:

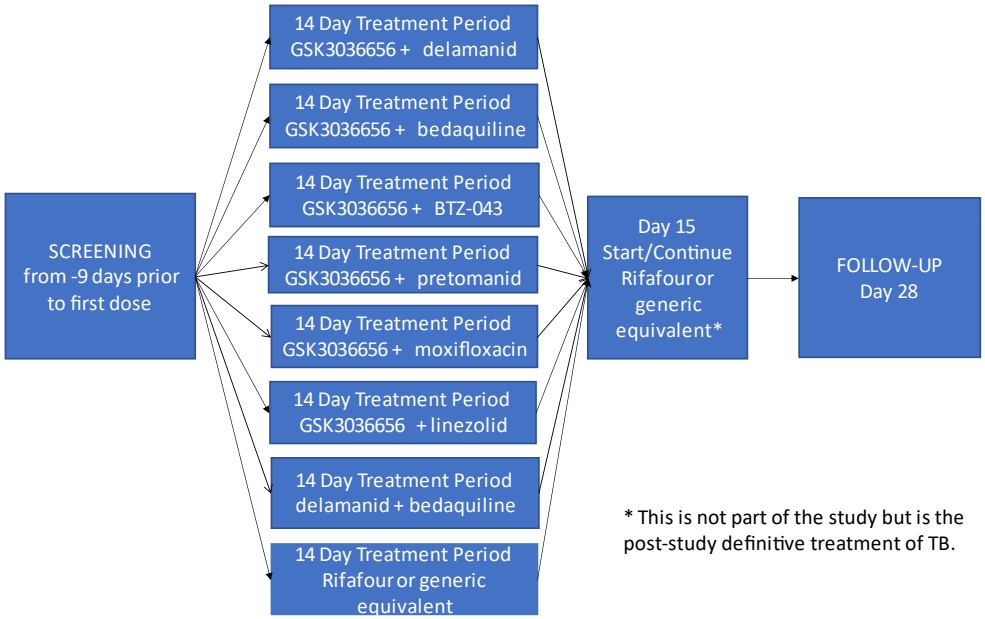
- Population: participants with a new, untreated episode of drug sensitive (rifampicin-susceptible) pulmonary tuberculosis.
- Treatment condition: GSK3036656+bedaquiline, GSK3036656+delamanid, GSK3036656+BTZ-043, GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin, bedaquiline+delamanid, or SoC given daily for 14 days.

- Variable/endpoint: Incidence of event.
- Summary measure: Number and Percentage of subjects with the event, within each treatment group.
- Intercurrent events:
  - Study treatment discontinuation – treatment policy strategy
  - Use of rescue medication – treatment policy strategy

Rationale for estimand: It is important to document all safety issues that could potentially be attributable to the regimen, irrespective of whether the participant completed the treatment regimen or received rescue treatment.

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• A single-centre, open-label trial in which subjects are randomised to one of eight treatment arms.
	• Via protocol amendments, treatment arms were included sequentially over 3 cohorts:
	  • Cohort 1: GSK3036656+bedaquiline, GSK3036656+delamanid, bedaquiline+delamanid and standard of care (SoC);
	  • Cohort 2: GSK3036656+BTZ-043 and SoC
	  • Cohort 3: GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin and SoC

<table>
<tr><td></td><td>

Up to 15 participants randomised to each of the GSK3036656+bedaquiline, GSK3036656+delamanid, GSK3036656+BTZ-043, GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin and bedaquiline+delamanid arms; up to 23 participants in total randomised to the standard-of-care arm (i.e. Rifafour e-275 or equivalent generic alternative).
Screening will be performed on days -9 to -1, followed by 14 days of once daily dosing and a follow-up visit 28 days after the first dose.
All laboratory staff involved in analysing and reporting the microbiological endpoints (CFU counts and TTP) will be blinded to treatment allocation.

</td></tr>
<tr><td>Study interventio n</td><td>
<table>
<tr><th>Study Intervention Name</th><th>Dosage formulation</th><th>Unit dose strength(s)/Dosage level(s)</th></tr>
<tr><td>GSK3036656</td><td>Capsule</td><td>5/25mg /20 mg (as free base equivalent)

Loading dose 50 mg on Day 1</td></tr>
<tr><td>Delamanid</td><td>Tablet</td><td>50/300 mg</td></tr>
<tr><td>Bedaquiline</td><td>Tablet</td><td>100/400 mg

Loading dose 700 mg on Day 1 and 500 mg on Day 2</td></tr>
<tr><td>BTZ-043</td><td>Tablet</td><td>250 mg/ 1000 mg</td></tr>
<tr><td>Moxifloxacin</td><td>Tablet</td><td>200 mg/ 400 mg</td></tr>
<tr><td>Pretomanid</td><td>Tablet</td><td>200 mg/ 200 mg</td></tr>
<tr><td>Linezolid</td><td>Tablet</td><td>200 mg/ 600 mg</td></tr>
<tr><td>Rifafour e-275 (or equivalent generic alternative)</td><td>Tablet</td><td>Standard dose: 150/75/400/275 mg of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol respectively per tablet</td></tr>
</table>
</td></tr>
<tr><td>Study interventio</td><td>

Following are the treatment groups:

GSK3036656 + delamanid

</td></tr>
</table>

n Assignment	➢ GSK3036656 + bedaquiline ➢ GSK3036656+BTZ-043 ➢ GSK3036656+pretomanid ➢ GSK3036656+linezolid ➢ GSK3036656+moxifloxacin ➢ Delamanid + bedaquiline ➢ Standard of care for DS-TB • All treatment groups with up to 15 participants in each group (apart from the SoC arm which contains up to 23 participants). • For treatment arms GSK3036656+bedaquiline, GSK3036656+delamanid, bedaquiline+delamanid arms and standard of care, participants randomly assigned (3:3:3:2) to one of the four arms. • For GSK3036656+ BTZ-043 and standard-of-care, participants assigned (5:1) to 1 of 2 arms. • For treatment arms GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin and standard-of-care, participants randomly assigned (3:3:3:2) to one of four arms.
Interim Analysis	Two interim analyses have been planned for this study. • Interim 1 The first Interim will be conducted after completion of all subjects in GSK3036656 + delamanid, GSK3036656 + bedaquiline, and Delamanid+bedaquiline arms prior to the completion of the other arms within the study. • Interim 2 The second Interim will be conducted after completion of all subjects in GSK3036656 + BTZ-043 arm.

2. STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested in this study.

The primary objective of this study is to estimate the early bactericidal activity (EBA) of GSK3036656, dosed in combination with either delamanid, bedaquiline, BTZ-043, pretomanid, moxifloxacin or linezolid. No between treatment group statistical comparisons are planned, though the results will be compared qualitatively. Within each treatment group a decrease in log10CFU from baseline to Day 14 is considered to indicate a treatment effect.

The SoC treatment arm is an established 4- drug combination. It is expected that the EBA of SoC treatment will be greater than that of the dual combinations being studied. The SoC arm is included to ensure the results are in-line with expectations, i.e. to provide qualitative internal assay sensitivity.

2.1. Multiplicity Adjustment

Multiplicity adjustment is not applicable for this study; no hypotheses are to be tested.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	Study Population
Enrolled	• All participants who passed screening and entered the study.	Study Population
Safety	• All participants who received at least 1 dose of study treatment. • Participants will be analysed according to the treatment they actually received.	Safety
Efficacy	• Participants in the safety population who provided a baseline and at least one post-baseline evaluable sputum sample. • Participants will be analysed according to the treatment they actually received.	EBA

CCI [redacted]

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Participants who withdraw early from the study will not be replaced.

Data will be summarised by treatment group. No quantitative between treatment group comparisons will be made. All confidence intervals (CIs) will be 2-sided 95% CIs and will be produced separately for each treatment group and cohort.

Whilst the randomisation is to be stratified by PET/CT scan eligibility, this is for safety purposes for this specific procedure. It is not believed to impact the EBA analyses; statistical analyses will not therefore include this stratification variable as a covariate.

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

For each of the PK parameters the following summary statistics will be calculated and tabulated:

- Untransformed data: N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum
- Log-transformed data: Geometric mean, 95% CI for the geometric mean, SD, between participant coefficient of variation (%CVb)

The numbers of subjects with intercurrent events, i.e. those withdrawing from study treatment and those requiring rescue therapy will be summarised by treatment group.

4.1.2. Baseline Definition

For the purpose of assessment of bacterial and imaging endpoints, the pre-treatment baseline will be defined as the mean of Day –2 and Day –1; if data is available at only Day –2 or Day –1, then that value used as baseline. For all other endpoints, baseline will be the last available pre-treatment assessment.

If baseline data is missing no derivation will be performed and baseline will be set to missing.

4.2. Primary Endpoint Analyses

4.2.1. Definition of endpoint/estimand

The primary endpoint is the change in log_{10}CFU from baseline to Day 14 (EBA CFU_{0-14}). The primary EBA estimand is described in Section 1.1. The efficacy analysis set will be used for analysis.

4.2.2. Main analytical approach

Model Specifications

A mixed model repeated measures analysis will be used to analyse the change from baseline to Day 14 in log_{10}CFU. The terms to be included in the model are:

- **Response**: log_{10}CFU
- **Categorical**: treatment
- **Continuous**: day, BMI, baseline
- **Interaction**: treatment*day and baseline*day
- **Random**: Subject

The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

An unstructured covariance structure for the G matrix will be used.

- If this model fails to converge, alternative covariance structures may be considered.
- Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

Where CFU plate counts are Too Numerous To Count (TNTC) a value of 2500 should be imputed.

All available data will be included in the model up until the point where a participant discontinues study treatment and/or receives rescue medication, i.e. a hypothetical strategy will be employed for these intercurrent events. Any bactericidal data collected after these events will be listed only.

Model Checking & Diagnostics

- All available data will be included in the model up until the point where a participant discontinues study treatment and/or receives rescue medication, i.e. a hypothetical strategy will be employed for these intercurrent events. Any bactericidal data collected after these events will be listed only.
- Normality assumptions underlying the statistical analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data (e.g. square root).

Model Results Presentation

Estimates of the mean change from baseline to Day 14, together with the SE and 95% confidence intervals, for each treatment group, will be presented. The results will be compared qualitatively, but no formal between treatment groups comparisons will be performed.

4.2.3. Additional Summaries and Figures

Change from baseline in log_{10}CFU will be summarised and plotted, by timepoint, for each treatment group, for the efficacy population.

4.3. Secondary Endpoints Analyses

4.3.1. Secondary EBA Endpoints

4.3.1.1. Definition of endpoints/estimands

The secondary EBA endpoint is the change in TTP from baseline to Day 14 (EBA TTP_{0-14}). Due to the skewed distribution of the TTP results, values will be log-transformed prior to summarising and analysis, i.e. $log_{10}TTP$ will be the response variable. The secondary EBA estimand is described in Section 1.1. The efficacy analysis set will be used for analysis.

4.3.1.2. Main analytical approach

The analysis of the change from baseline to Day 14 in TTP will be analogous to that described for the primary EBA endpoint, change from baseline to Day 14 in $log_{10}CFU$, described in Section 4.2.2, replacing the response variable ($log_{10}CFU$) with $log_{10}TTP$.

All available data will be included in the model up until the point where a participant discontinues study treatment and/or receives rescue medication, i.e. a hypothetical strategy will be employed for these intercurrent events. Any bactericidal data collected after these events will be listed only.

4.3.1.3. Sensitivity analyses

No sensitivity analysis has been planned for the secondary EBA endpoint.

4.3.1.4. Additional Summaries and Figures

Change from baseline in $log_{10}TTP$ will be summarised and plotted, by timepoint, for each treatment group, for the efficacy population.

4.3.2. Secondary Safety Endpoints

4.3.2.1. Definition of endpoints/estimands

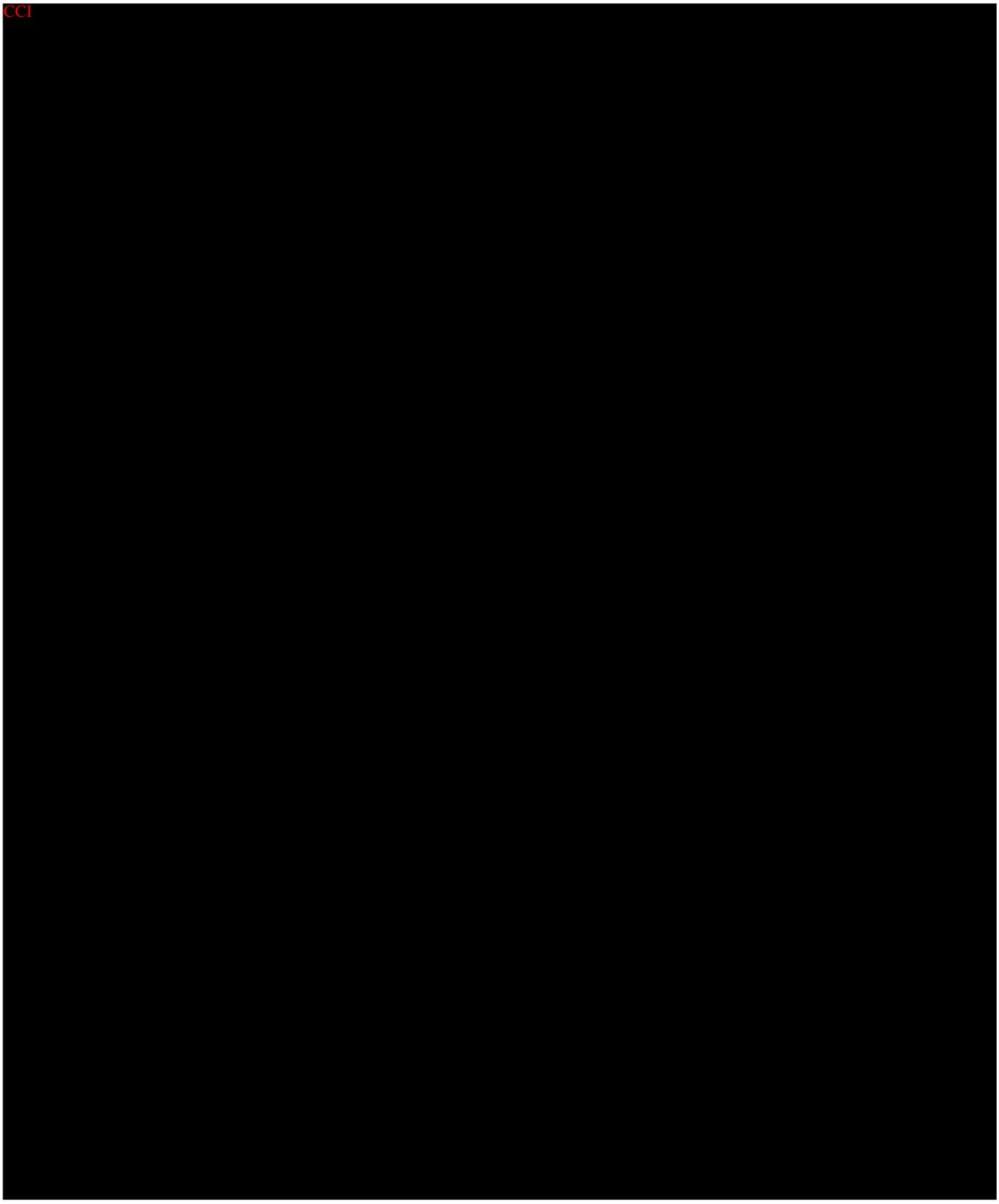
The secondary safety endpoints are as follows:

1. Incidence of serious adverse events.
2. Incidence of adverse events of grade 3 severity or higher.
3. Incidence of adverse events considered by the investigator to be possibly, probably or definitely related to study drug.
4. Incidence of participants withdrawn from the treatment/study due to adverse events.
5. Incidence of electrocardiogram (ECG) values of potential clinical importance (PCI).
6. Incidence of clinical chemistry laboratory values of PCI.
7. Incidence of haematology laboratory values of PCI.
8. Incidence of vital signs parameters of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) of PCI.

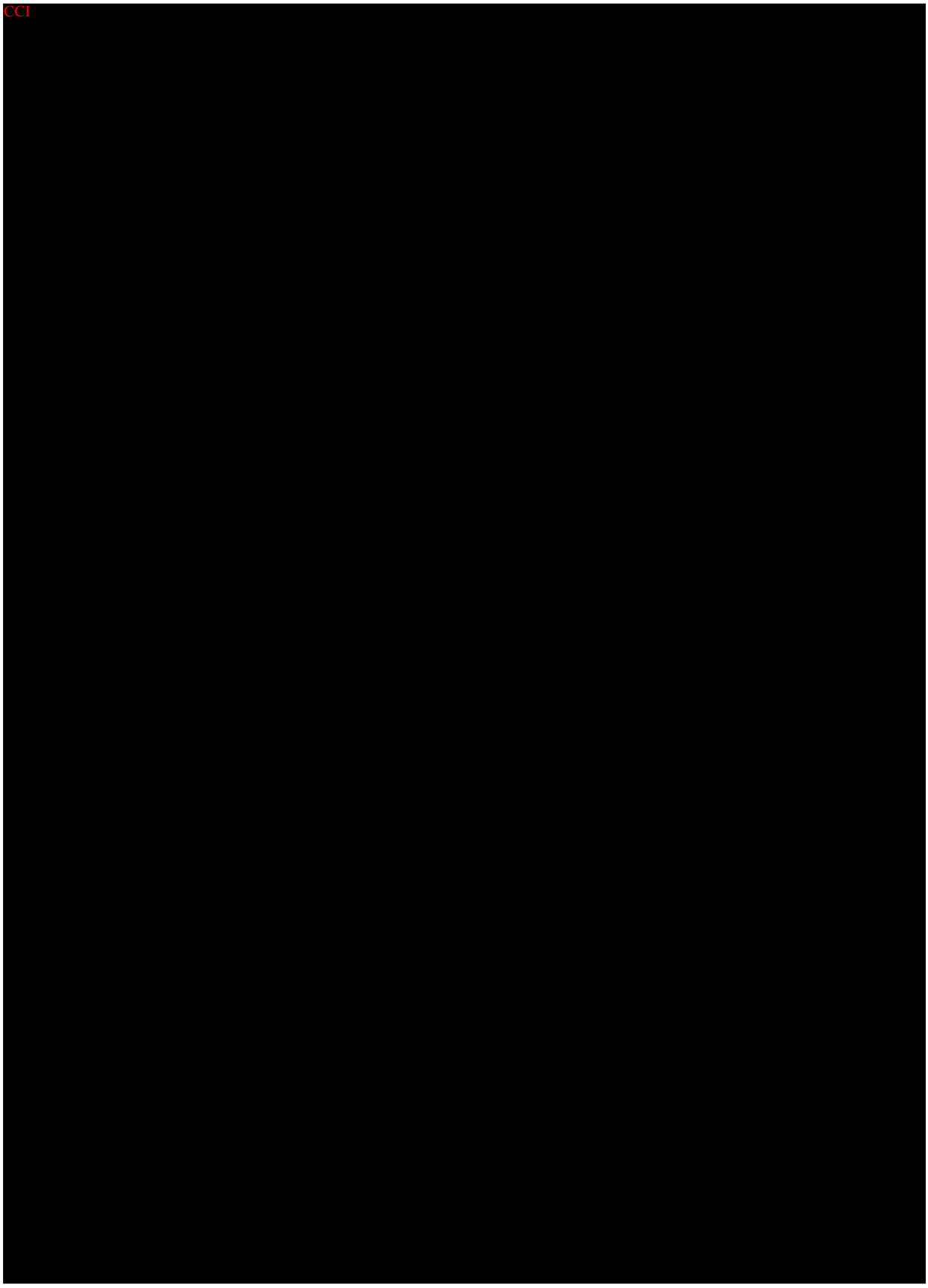
The secondary safety estimand, the attributes of which are applicable to all secondary safety endpoints, is described in Section 1.1. The safety analysis set will be used for analysis.

Further details regarding the reporting of these secondary safety endpoints are provided in Section 4.5.

CCI



CCI





4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.5.1. Extent of Exposure

- Descriptive summary of extent of exposure will be presented for each treatment.
- Details of the planned displays are provided in Output programming specifications (OPS).

4.5.2. Adverse Events

An adverse event (AE) is considered study intervention emergent if the AE onset date is on or after study intervention start date.

All AE summaries will be based on study intervention emergent events unless otherwise specified. SAE summaries will be based on all SAEs reported regardless of whether they meet the definition of study intervention emergent or not. All AE and SAE summaries will be by System Organ Class (SOC) and Preferred Term (PT) only unless otherwise specified.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary) [and graded by the investigator according to the NCI-CTCAE, (version 4.03)]. Counting of AEs will be based on the number of participants, not the number of AEs.

In addition to all adverse events, there will be separate summaries for:

i. Serious AEs
ii. Severe AEs (AEs with a grade of 3 or higher)
iii. Drug-related AEs
iv. AEs leading to study withdrawal
v. AEs leading to study treatment discontinuation

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

The following laboratory endpoints will be assessed:

- Haematology parameters (including Platelet count, RBC count, Hemoglobin, Hematocrit, Coagulation Test (INR, PT, APTT), RBC Indices (Mean corpuscular volume (MCV), Mean corpuscular Hemoglobin (MCH), %Reticulocytes), WBC count (Lymphocytes, Neutrophils, Monocytes, Eosinophils, Basophils)).
- Clinical chemistry parameters (including Blood urea nitrogen (BUN), Potassium, Sodium, Creatinine, Glucose(random/fasting), Total Bilirubin, AST, GGT, LDH, ALT, sodium, potassium, calcium (corrected for albumin), chloride, Alkaline phosphatase, Total Protein, Albumin, Magnesium.
- Urinalysis parameters (Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. Microscopic examination (if blood or protein is abnormal)).
- The change from baseline in all haematology and clinical chemistry laboratory endpoints will be summarized descriptively by visit and treatment.
- A summary will present the worst case post-baseline data, relative to baseline data, by PCI category, for each participant.

The values of PCI are provided in Section 6.2.1.1.

Details of the planned displays are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

4.5.3.2. Vital Signs

The following vital signs endpoints will be presented by visit and treatment group.

- Temperature
- Heart rate
- Respiratory rate
- Systolic and diastolic blood pressure
- Change from baseline will be presented by visit and treatment group

- Vital sign data (SBP, DBP and HR), relative to PCI criteria, will be summarized by treatment group, vital sign and category. The summary will present the worst-case post baseline data, relative to baseline data, by PCI category, for each participant.

The values of PCI are provided in Section 6.2.1.1.

Details of the planned displays are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

4.5.3.3. ECG

The following endpoints will be presented by visit and treatment group.

- Heart Rate
- PR interval
- QRS Duration
- Uncorrected QT Interval
- QTcB and QTcF
- QT & QTc intervals
- Summary tables will be provided for
  - ECG findings,
  - ECGs change from baseline values,
  - Maximum post-baseline QTc values relative to baseline values
  - Maximum increase in post-baseline QTc values relative to baseline values
- ECG values relative to PCI criteria, will be summarized by treatment group, ECG parameter and category. The summary will present the worst case post-baseline data, relative to baseline data, by PCI category, for each participant.

The values of PCI are provided in Section 6.2.1.1.

Details of the planned displays are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

4.5.3.4. Echocardiograms

The change from baseline in echocardiograms endpoints will be summarized descriptively by visit and treatment.

4.6. Other Analyses

4.6.1. Subgroup analyses

No formal subgroup analyses are planned for this study.

4.6.2. Other variables and/or parameters

Not Applicable.

4.7. Interim Analyses

Two interim analyses have been planned for this study.

Interim 1

The first Interim will be conducted after completion of all subjects in the Cohort 1 arms, but prior to the completion of the other arms within the study. Data from these three arms, together with that from subjects recruited to the SoC arm during this first cohort, will be included in the interim analysis. Data from other treatment arms, or that from SoC subjects recruited in cohorts 2 and 3 will be excluded, even if available at the time of the data cut.

The safety, efficacy and PK data from the GSK3036656 + delamanid and GSK3036656 + bedaquiline arms of 214912 would be informative for the UNITE4TB Ph2b/c study (PARADIGM4TB). PARADIGM4TB will assess the efficacy and safety of multiple GSK3036656 4-drug regimens, all of which include bedaquiline, and 3 out of 4 include delamanid.

There are no plans to make any decisions regarding the ongoing 214912 trial from the interim analysis, however, the results will help to inform the regimens to be included in the planned Ph2b/c PARADIGM4TB study. If clinically significant antagonism is observed when giving GSK3036656 with either bedaquiline or delamanid, then bedaquiline or delamanid sparing GSK3036656 regimens may need to be included in the PARADIGM4TB study. No fixed decision rules are to be applied, but the EBA data (CFU and TTP) will be considered, alongside that from the bedaquiline+delamanid arm within this study, and the GSK3036656 monotherapy data from study 201214. Available in-vitro and in-vivo data will also be considered.

Interim 2

The second interim will be conducted after completion of all subjects in GSK3036656 + BTZ-043 arm. Data from this arm, together with that from subjects recruited to the SoC arm during both this second cohort and cohort 1, and data from the previously completed GSK3036656+delamanid, GSK3036656+bedaquiline and delamanid+bedaquiline arms will be included in the second interim analysis. Data from other treatment arms, or that from SoC subjects recruited in cohort 3 will be excluded, even if available at the time of the data cut.

Similarly, to the first interim analysis, results from this second interim will help to inform on the inclusion of a four drug regimen containing BTZ-043 and GSK3036656 in the Phase 2B/C UNITE4TB PARADIGM4TB study.

4.8. Changes to Protocol Defined Analyses

The change to the originally planned statistical analysis specified in the Protocol Amendment 4 (June 2024) is mentioned below:

Protocol	SAP	Rational
CCI [redacted]		
Section 8.2: Microbiological Efficacy/Activity Assessments	Section 4.3.1 Secondary EBA Endpoints	TTP data is positively skewed and log_{10}TTP will be used in the summaries and analysis.
Section 9.2 Analysis Sets: Definition of the Efficacy Analysis Set: Participants in the safety population who provided a baseline and at least one post-baseline evaluable sputum sample. Participants will be analysed according to the treatment they *were randomised to.*	Section 3 Analysis Sets: Definition of the Efficacy Analysis Set is updated to: Participants in the safety population who provided a baseline and at least one post-baseline evaluable sputum sample. Participants will be analysed according to the treatment they *actually received.*	The definition of the Efficacy analysis set has been amended to account for participants who were administered the wrong treatment for the duration of the trial. Given this is a Ph2a study where it is important to understand the bactericidal activity of each dual combination, participants will be analysed according to the treatment they received.

5. SAMPLE SIZE DETERMINATION

Up to 15 participants enrolled into each of the GSK3036656+bedaquiline, GSK3036656+delamanid, GSK3036656 + BTZ-043, GSK3036656 + pretomanid, GSK3036656 + linezolid, GSK3036656 + moxifloxacin and bedaquiline+delamanid arms until at least 12 have completed the 14-day assessments.

Up to 23 participants enrolled into the standard of care arm. For purposes of randomization, the SoC treatment arm will be split into 3 parts. Up to 10 participants will be enrolled into the standard of care arm during each of the first and third cohorts, until at least 8 have completed the 14 day assessments. 3 participants will be enrolled into the second standard of care arm. This is to ensure there is a concurrent control for all arms.

The following table describes the precision of a 2 sided 95% confidence interval (CI), for the mean change in $log_{10}CFU_{(0-14)}$, for differing numbers of subjects per treatment group, based on the normal distribution, and a standard deviation of 0.6.

This includes an example of the confidence interval where the mean change in $log_{10}CFU_{(0-14)}$ is -1.2, the anticipated change for subjects treated with GSK3036656 as monotherapy. Of note the standard deviation has been estimated based on the results of a MMRM analysis of observed data for subjects treated with GSK3036656 monotherapy. The variability and the pattern of missing data is expected to be similar in this study as that observed during the monotherapy study.

Number of Subjects#	Standard Error*	Distance from mean to 95% CI limits*	Example 95% CI (mean change in $log_{10}CFU_{(0-14)}$ = -1.2)*
8	0.21	0.42	(-1.62, -0.78)
10	0.19	0.37	(-1.57, -0.83)
12	0.17	0.34	(-1.54, -0.86)
15	0.15	0.30	(-1.50, -0.90)
#All available data from subjects enrolled and included in the efficacy population will be included in the MMRM. analysis *CFU data is interpreted on the log scale.			

5.1. Sample Size Sensitivity

If the standard deviation is greater than anticipated, the 95% CIs for the mean change from baseline to Day 14 in $log_{10}CFU$ will be less precise than described above. The following table describes the precision of the 95% CIs for standard deviations of 0.8 and 1.

Number of Subjects#	Standard Deviation*	Standard Error*	Distance from mean to 95% CI limits*	Example 95% CI (mean change in $log_{10}CFU_{(0-14)}$ = -1.2)*
8	0.8	0.28	0.55	(-1.75, -0.65)
10	0.8	0.25	0.50	(-1.70, -0.70)
12	0.8	0.23	0.45	(-1.65, -0.75)
15	0.8	0.21	0.40	(-1.60, -0.80)
8	1.0	0.35	0.69	(-1.89, -0.51)
10	1.0	0.32	0.62	(-1.82, -0.58)
12	1.0	0.29	0.57	(-1.77, 0.63)
15	1.0	0.26	0.51	(-1.71, -0.69)
#All available data from subjects enrolled and included in the efficacy population will be included in the MMRM analysis *CFU data is interpreted on the log scale.				

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

A summary of the number of participants in each of the participant level analysis sets will be provided for the Screened analysis set. The Safety analysis set will be used for all other study population analyses unless otherwise specified.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including gender, age, ethnicity, height/weight at screening, BMI, smoking status and treatment history and race will be summarized with descriptive statistics.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized by treatment.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. However, the summary will be based on GSK Drug dictionary only.

The use of rescue medications during the study is an intercurrent event. Any potential rescue medications used during the study will be identified following a review of all concomitant medications by the GSK medical monitor. Any medications considered to be treatments for TB will be flagged.

The summary of concomitant medications will be provided by ingredient, i.e. multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e. ingredients with the same base name but different salt will appear under one base name in the summary. Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary.

Concomitant medications include any medication that was taken during the on intervention period.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

6.2.1.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Change from Baseline	Decrease of 0.075	
Haemoglobin	g/L	Male	75	180
		Female	75	180
		Change from Baseline	Decrease of 25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Calcium	mmol/L		2	2.75
Creatinine	%	Change from Baseline		Increase of 30%
Glucose	mmol/L		3	11
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT	IU/L	High	≥ 3x ULN
AST	IU/L	High	≥ 3x ULN
T Bilirubin	µmol/L	High	≥ 1.5x ULN

ULN = Upper Limit of Normal; ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase;
T. Bilirubin=Total Bilirubin

6.2.1.2. ECG Values

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTcF Interval	msec		>450
Absolute PR Interval	msec	< 110	>220
Absolute QRS Interval	msec	< 75	>110
Change from Baseline			
Increase from Baseline QTcF	msec		>60

QTcF=QT Interval corrected for heart rate (Fridericia); PR=Electrocardiographic PR Interval

6.2.1.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	>160
Diastolic Blood Pressure	mmHg	< 45	>100
Heart Rate	bpm	< 40	>110
Respiratory Rate	Breaths/min	10	28
Temperature	Degrees C	35.0	37.9

6.2.2. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-Intervention is defined as time prior to the first dose of study intervention.

On-Intervention is defined as time from first dose to last dose plus 7 days. If time of assessment or study intervention is not collected, the following assessment on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-intervention: ECG, Lab, and vital signs, and first dose date is considered on-intervention for AE and concomitant medication.

Post-Intervention is defined as any time post on-intervention window, i.e. > last dose date + 7 days.

6.2.3. Study Day and Reference Dates

The reference date is the study intervention start date and will be used to calculate study day for safety and bactericidal measures.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.4. Assessment Window

For data summaries by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a target visit based on visit window defined in the table below. If there are multiple assessments within the same window, a scheduled visit will be prioritized over un-scheduled visits. If all assessments within the same window are from unscheduled visits, the earliest one will be taken in the slotting.

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Safety, Efficacy	All	Day -3	Day -9	Day -3	Screening
Safety, Efficacy	All	Day -2	Day -2	Day -2	Day -2, Screening
Safety, Efficacy	All	Day -1	Day -1	Day -1	Day -1, Screening
Safety, Efficacy	All	Day 1	Day 1	Day 1	Day 1
Safety, Efficacy	All	Day 2	Day 2	Day 2	Day 2
Safety, Efficacy	All	Day 3	Day 3	Day 3	Day 3
Safety, Efficacy	All	Day 4	Day 4	Day 4	Day 4
Safety	All	Day 5	Day 5	Day 5	Day 5
Safety, Efficacy	All	Day 6	Day 6	Day 6	Day 6
Safety	All	Day 7	Day 7	Day 7	Day 7
Safety, Efficacy	All	Day 8	Day 8	Day 8	Day 8
Safety	All	Day 9	Day 9	Day 9	Day 9
Safety, Efficacy	All	Day 10	Day 10	Day 10	Day 10
Safety	All	Day 11	Day 11	Day 11	Day 11
Safety, Efficacy, PK	All	Day 12	Day 12	Day 12	Day 12
Safety, PK	All	Day 13	Day 13	Day 13	Day 13
Safety, Efficacy, PK	All	Day 14	Day 14	Day 14	Day 14
Safety, PK	All	Day 15	Day 15	Day 15	Day 15
Safety	All	Day 28	Day 21	Day 35	Day 28

NOTES:
For data summarised by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a scheduled visit window, if no competing visit exists within the window. If there are multiple assessments within the same window which are not unscheduled visits, the earliest results will be used in the summaries.

6.2.5. Multiple measurements at One Analysis Time Point

When triplicate ECG or Vital Sign assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessments.

For the Vital Signs assessment data collected at the planned screening visit, only the date was recorded, without the specific time. If participants had two additional unscheduled vital sign readings (with times recorded), the average of all three readings will be calculated and included in the summary tables. This approach will be used even though it is not possible to verify whether the unscheduled readings occurred within the protocol-specified interval of at least 1 minute but no more than 5 minutes apart from the planned reading.

6.2.6. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events).
Adverse Events	• Partial dates for AEs recorded in the CRF will be imputed using the following conventions:

<table>
<tr><th>Element</th><th colspan="2">Reporting Detail</th></tr>
<tr><td></td><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
o If month and year of start date = month and year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
▪ Else set start date = study intervention start date.
o Else set start date = 1st of month.</td></tr>
<tr><td></td><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
o If year of start date = year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
▪ Else set start date = study intervention start date.
o Else set start date = January 1.</td></tr>
<tr><td></td><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td></td><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td></td><td>Completely missing start/end date</td><td>No imputation</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td colspan="2">• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:</td></tr>
<tr><td></td><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
o If month and year of start date = month and year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
▪ Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td></td><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:</td></tr>
</table>

Element	Reporting Detail		
		○ If year of start date = year of study intervention start date, then ▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. ▪ Else set start date = study. intervention start date. Else set start date = January 1.	
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).	
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.	
	Completely missing start/end date	No imputation	

Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

7. REFERENCES

Bland, M., Altman, D., Measuring agreement in method comparison studies, Statistical Methods in Medical Research, 1999.

ICH Harmonized Guideline; Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guidelines on Statistical Principles for Clinical Trials E9(R1), November 2019

Signature Page for 214912 TMF-14499679 v4.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 18-Jun-2025 10:32:57 GMT+0000

Signature Page for TMF-14499679 v4.0