TITLE PAGE

Primary study intervention(s): GSK3036656

Other study intervention(s): delamanid
bedaquiline
ethambutol/pyrazinamide/isoniazid/rifampicin
BTZ-043
linezolid
moxifloxacin
pretomanid

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.

Protocol Number 214912/ Amendment 04

Compound Number or Name: GSK3036656

Brief 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.

Study Phase: Phase 2

Sponsor Name and Legal Registered Address:

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Approval Date 18 Jun 2024

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 4	18 Jun 2024
Amendment 3	17 August 2023
Amendment 2	13 January 2023
Amendment 1	05 October 2022
Original Protocol	14 December 2021

Amendment 4 18 Jun 2024

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

As the treatment arms that include delamanid, bedaquiline and BTZ-043 have completed, inclusion and exclusion criteria and assessments outlined in the SoA specific to these drugs have been removed from the protocol.

CCI [redacted]
CCI [redacted]
CCI [redacted]

Identified in the table below are substantial changes made to the Study Protocol since the previous submitted version.

List of main changes in the protocol and their rationale:

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Haem/chem/urinalyses assessments removed from Day 11.	This was a requirement for the BTZ-043 arm only which has completed.
Section 1.3 Schedule of Activities	PK Microsampling: Note added to confirm these samples do not need to be collected for the GSK3036656 + pretomanid, GSK3036656 +moxifloxacin or GSK3036656 + linezolid arms.	PK microsampling is not required for the GSK3036656 + pretomanid, GSK3036656 +moxifloxacin or GSK3036656 + linezolid arms as the required number of microsampling PK samples has been achieved within the previous study arms.
Section 2.3.1 Risk Assessment	Updated the criterion for creatinine clearance to ≥75mL/min.	The criterion of CrCl ≥90mL/min applied to the GSK3036656 + BTZ-043 arm which has completed.
Section 2.3.1 Risk Assessment	Footnote added to confirm that risks associated to bedaquiline, delamanid and/or BTZ-043 are not applicable for the GSK3036656 + pretomanid, GSK3036656 +moxifloxacin or GSK3036656 + linezolid arms	Risks relating to delamanid, bedaquiline and/or BTZ-043 are no longer applicable with the remaining arms.
Section 5.1 Inclusion Criteria, Type of Participant and Disease Characteristics	Updated the criterion for creatinine clearance to ≥75mL/min.	The criterion of CrCl ≥90mL/min applied to the GSK3036656 + BTZ-043 arm which has completed.
Section 5.2 Exclusion Criteria Medical Conditions	Deleted exclusion criterion #5: Arterial hypertension with Systolic BP >=160 mm Hg or diastolic BP >=100 nm Hg.	This only applied to the GSK3036656 + BTZ-043 arm which has completed.
Section 5.2 Exclusion Criteria/Medical Conditions	Exclusion criteria changed to allow HIV infected participants to be enrolled providing they had not received efavirenz or lopinavir-boosted ritonavir as antiretroviral therapy medication within the last 30 days	Updated due to completion of GSK3036656 + BTZ-043 arm.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria/Medical Conditions	Removed exclusion criterion #13 a. "Removal of serum potassium grade 2 or greater (<3.0 mEq/L)" b. "serum magnesium <0.5mmol/L"	Removed as all treatment arms including delamanid and bedaquiline have been completed.
Section 5.2 Exclusion Criteria/Medical Conditions	Updated exclusion criterion #20 to remove bedaquiline, delamanid and BTZ-043.	Removed as all treatment arms including delamanid and bedaquiline have been completed.
Section 5.2 Exclusion Criteria/Medical Conditions	Added exclusion criterion #23 to exclude lactose intolerance or deficiency.	Updated due to inclusion of pretomanid.
Section 5.3.1, Meals and Dietary Restrictions	Removed apple juice and orange juice from the list of restrictions.	These were excluded due to BTZ-043 and that arm of the study has completed.
CCI [redacted]		
Section 10.9 Appendix 9 Protocol Amendment History	Addition of overall rationale for previous amendment.	

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1. PROTOCOL SUMMARY

1.1. Synopsis

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.

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

Rationale: With drug-resistance becoming increasingly prevalent for tuberculosis (TB), all-new drug combinations that avoid existing resistance are urgently needed. GSK3036656 is a compound under development with a novel mechanism of action for the treatment of TB. It suppresses protein synthesis in *Mycobacterium tuberculosis* (Mtb) by selectively inhibiting the enzyme Leucyl t-RNA synthetase and is currently under investigation in a monotherapy 14 day early bactericidal activity (EBA) study. The Click-TB consortium, funded by the European Union, are performing a series of dual combination EBA studies. GSK3036656 will be included in this series. The studies will incorporate novel radiological and immunological TB biomarkers to complement traditional sputum microbiological readouts.

While the monotherapy study will have established proof-of-principle of antituberculosis activity of GSK3036656, this will be the first study where GSK3036656 is dosed in combination with other TB drugs, including the drug candidate BTZ-043, a benzothiazinone DprE1 inhibitor. The study will provide safety and tolerability data that will inform future combination studies with GSK3036656. EBA studies have been considered a fundamental component of the early assessment of anti-tuberculosis drugs in man. However, there may be potential to improve the predictivity of an EBA to longer term relapse outcomes. Combining the EBA readout with immunological and radiological biomarkers may enable this. The data from this study will also be integrated with that from other studies; a statistical model will be developed combining microbiological and biomarker readouts of all dual combination EBA studies within Click-TB with the intent of better predicting future long term pivotal outcomes and to understand the contribution of each single drug in its respective combinations. The model will then rank the drug combinations with the greatest benefit:risk profile from which those with potential safety concerns will be removed. The most promising regimens will be taken forward into a longer study, with the aim of identifying a novel regimen for TB in addition to validating the statistical model.

Objectives and Endpoints and Estimands:

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 or 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.

Objectives	Endpoints
	• 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.
[1] Time to sputum-culture positivity is the time between sample inoculation and detection of mycobacterial growth.	

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 will be used as baseline. For all other endpoints, baseline is the last pre-treatment assessment.

Primary EBA Estimand

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+moxifloxacin, GSK3036656+linezolid 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:

- 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+moxifloxacin, GSK3036656+linezolid, 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 $CFU_{0\text{-}14}$).
- 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.

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 and will use the same strategies for the intercurrent events.

Safety Estimand

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+moxifloxacin, GSK3036656+linezolid, 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.

Overall Design:

The study will be randomized but not blinded (i.e., it will be 'open-label') with neither participant nor investigator blinded to treatment. Due to the different assessments being conducted for the SoC arm compared to the investigational regimens (no PET-Scans or PK sampling), and the additional burden to patients if a double-dummy design were to be employed, the blinding of participants and the investigator was not considered feasible. Study participants will have been diagnosed with drug-sensitive TB and will revert to the standard treatment for TB (i.e. Rifafour e-275 or equivalent generic alternative) once the study treatment (Day 1 to Day 14) has been completed. To minimise bias, all laboratory staff involved in analysing and reporting the microbiological endpoints (log10CFU counts and TTP) will be unaware of treatment assignments. Study participants will remain in the clinic as in-patients for the 14 day treatment duration.

Brief Summary:

The purpose of this study is to measure the early bactericidal activity, safety and tolerability with GSK3036656 in combination with either delamanid, bedaquiline, BTZ-043, pretomanid, moxifloxacin or linezolid, or delamanid in combination with bedaquiline or standard of care in participants with drug-sensitive pulmonary tuberculosis.

Study details include:

- The study duration will be up to 5 weeks.
- The treatment duration will be up to 2 weeks.
- The visit frequency will be up to 1 week for screening, 2 days of baseline sputum sample collection, 2 weeks of inpatient treatment and 1 day for the final follow-up visit.

Number of Participants: Up to 128 participants will be enrolled to study intervention.

Note: Enrolled means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Intervention Groups and Duration:

The approximate duration of the study for an individual participant is anticipated to be 5 weeks to include a maximum of 1 week for screening, 2 days of baseline sputum sample collection, 2 weeks of inpatient treatment and another 2 weeks as outpatients until the final follow-up visit.

Up to 8 treatment groups with up to 15 participants in each group (apart from the SoC arm which will contain up to 23 participants). Participants already randomized to GSK3036656+bedaquiline, GSK3036656+delamanid, bedaquiline+delamanid and Standard of care (SoC) were assigned with a ratio of 3:3:3:2 to 1 of 4 arms. Participants will be randomized to GSK3036656+BTZ-043 and SoC with a ratio of 5:1 to 1 of the arms. Participants will be randomized to GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin and Standard of Care (SoC) with a ratio of 3:3:3:2 to 1 of 4 arms.

Randomisation will be stratified by eligibility for a PET-CT scan:

- GSK3036656 20 mg once daily + delamanid 300 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1.

- GSK3036656 20 mg once daily + bedaquiline 400 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1. A loading dose of 700mg bedaquiline will be given on Day 1 and 500 mg on Day 2. Participants will receive 400 mg bedaquiline on Days 3 to 14.

- GSK3036656 20 mg once daily + BTZ-043 1000 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1

- GSK3036656 20 mg once daily + pretomanid 200 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1.

- GSK3036656 20 mg once daily + moxifloxacin 400 mg once daily for 14 days. A loading dose of 50mg GSK3036656 will be given on Day 1.

- GSK3036656 20 mg once daily + linezolid 600 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1.

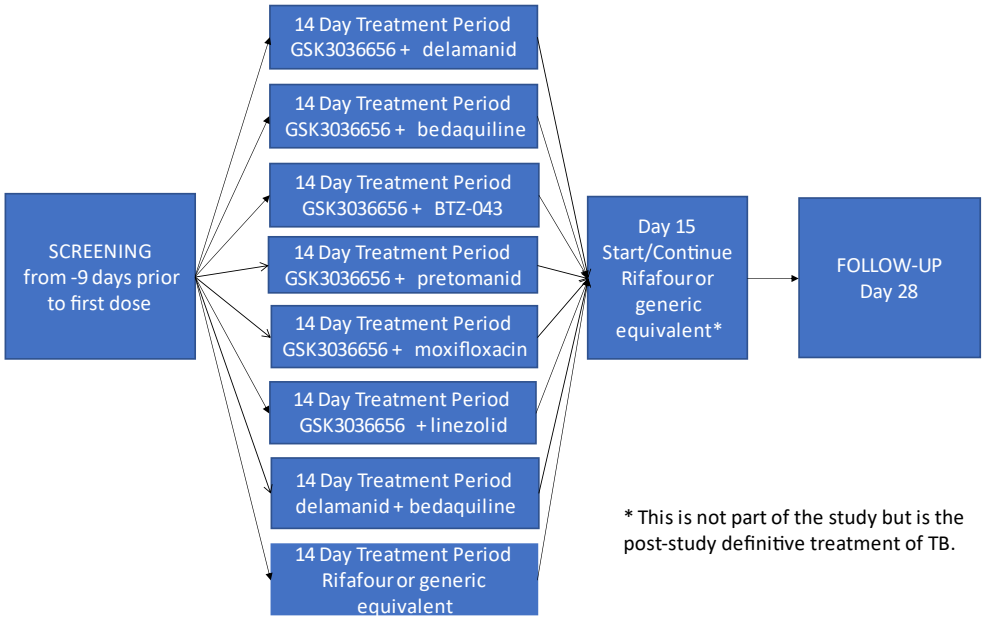
- Delamanid 300 mg once daily + bedaquiline 400 mg once daily for 14 days. A loading dose of 700 mg bedaquiline will be given on Day 1 and 500 mg on Day 2. Participants will receive 400 mg bedaquiline on Days 3 to 14.

- Standard of care for DS-TB (i.e. Rifafour e-275 or equivalent generic alternative) once daily for 14 days.

The Rifafour e-275 (or equivalent generic alternative) treatment group is included as a benchmark for the EBA quantitative mycobacteriology and to evaluate whether Isoniazid/Rifampicin/Pyrazinamide/Ethambutol (HRZE) in this population gives similar EBA results to that demonstrated in prior studies with this combination. A negative control arm, where subjects are left untreated, would be unethical due to the availability of effective treatment and the consequences of not treating TB.

Data Monitoring/ Other Committee: No

1.2. Schema



1.3. Schedule of Activities (SoA)

Supplementary study conduct information not mandated to be present in this protocol is provided in the Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not impact participant safety.

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- The Competent Authority (CA) and Ethics Committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

Procedure	Screening			Intervention Period						Follow-Up		Notes
	Visit											E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
Informed Consent	X											
Inclusion and Exclusion Criteria	X											Recheck clinical status before 1st dose of study medication.
Demography (includes Smoking History)	X											
Physical Examination	X			X	X	X	X	X	X	X	X	Height (m) will only be collected once at Visit 1 (day -9 to -3). A full physical examination will be performed at Visit 1 (day -9 to -3), with symptom-directed (brief) physical examinations at Visit 17 (day 14), Visit 19 (day 28) and Early Withdrawal Visit (EWV). Symptom directed physical examinations may be conducted as required during the study (visits 4 to 16). An assessment of the skin will be undertaken as part of the Screening (Visit 1),Visit 17 (Day 14) and Visit 19 (Day 28) physical examinations. Requirements for the physical examination and skin assessments are specified in the SRM
Medical & Treatment History	X											

Procedure	Screening			Intervention Period						Follow-Up		Notes
	Visit											E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
Hospital Admission	X	X										Participants can proceed with the Visit 2 (day -2) assessments as soon as their Visit 1 (day -9 to -3) assessments have been completed i.e. Visits 1 and 2 may occur on the same day as long as the screening results are available in time for randomisation. Participants may be hospitalised during the entire pre-treatment period if the Investigator considers it advisable for reasons of safety or compliance.
Enrolment		X										May occur once all screening results are available
Investigational product (IP) Administration and Compliance Check				X	X	X	X	X				After first dose of IP, subsequent doses will be administered 23 to 25 hours after the previous dose.
Hospital Discharge									X		X	
Safety Assessments												
Haem/Chem/Urinalysis	X			X	X*	X			X	X	X	*Safety blood samples and urinalysis will be collected at Visit 1, and Days 1, 3 (or 4), 8,15 and 28.
Urine Drug Screen	X	X										Urine drug screen: cocaine, amphetamines and opiates. Urine drug screen can be repeated at Visit 2 (day -2) for participants who were not hospitalized at Visit 1 (day -9 to -3)
HIV (and CD4 Count if HIV confirmed),	X											

Procedure	Screening			Intervention Period						Follow-Up	Notes
	Visit										E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
Hepatitis B and C Screening	X											
FSH + Estradiol	X											As needed, in women of non child bearing potential only
Vital Signs	X		X	X	X	X	X	X	X	X	X	Systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg), to include heart rate (beats per minute [bpm]), body temperature (°C), respiratory rate (breathes per minute) and weight (kg (weight to be taken at Screening only)). To be performed within 4 hours prior to the first daily dosing on Visit 4 (day 1) through to Visit 17 (day 14) and within 4 hours before the time dosing would have occurred on Visit 18 (day 15). For participants randomised to an arm containing BTZ-043, post-dose measurements of blood pressure and heart rate shall be performed at 1h, 2h, 6h post dose.(± 15 min) after at least 10 min supine rest. On days where the following assessments are done the order should be: vital signs before blood draws for pharmacokinetics (PK) or safety assessments.

Procedure	Screening			Intervention Period						Follow-Up	Notes
	Visit										E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
12-Lead Electrocardiogram (ECG)	T				X		X	X		X	X	ECGs to be taken in triplicate at Screening, and as single ECGs on Day 6, Day 10, Day 14, Day 28 and E.D. If an ECG demonstrates a prolonged QT interval, a further 2 ECGs should be obtained. T = Triplicate
Pregnancy Test	X			X	X	X			X	X*		Highly sensitive pregnancy test (serum) to be performed at Screening, (then urine-based test atVisit 4 (Day 1) prior to dosing, Visit 6 or 7 (Day 3 or 4), Visit 11 (Day 8), Visit 18 (Day 15 prior to discharge) and at the follow up Visit*(at Day 28+7, not earlier than Day 28). *If a urine test cannot be confirmed as negative, a serum pregnancy test is required.
Visual Assessment	X											Visual acuity, Ishihara test and Ocular history to be performed at Screening prior to dose administration, for all participants.

Procedure	Screening			Intervention Period						Follow-Up		Notes
	Visit											E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
Study Specific Assessments												
Chest X-Ray	X											
Echocardiogram	X							X			X*	Screening Echocardiogram may be taken on visit 1 (day -9 to -3), 2 (day -2) or 3 (day-1). Echocardiogram may be taken on Day 14 ± 1 day for logistical reasons *Every effort should be made to obtain Echocardiogram on participants who withdraw after Day 7 or on participants with changes in clinical status warranting a follow-up echo in the opinion of the investigator.
FDG-PET/CT		X						X				PET-CT scans will not be performed for the standard of care arm. Imaging cohorts only (participants aged 25-65 years, women of non-childbearing potential): FDG-PET/CT will be done on day-2 or day -1 visit, or before IP is administered on day 1. All other screening tests to be complete and study eligibility to be confirmed prior to conduct of first PET scan. Day 14 FDG-PET/CT has a ±3 day window, but every effort should be made to perform the PET/CT within ±1 day of the nominal Time, (i.e. Day 14).
Serum Biomarkers				X	X			X			X	Serum collected for biomarkers as follows: at day 1 before the first IP dosing, days 3, 7, 14 and E.D

Procedure	Screening			Intervention Period						Follow-Up	Notes
	Visit										E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
Urine Biomarkers				X	X			X			X	Urine collected for biomarkers as follows: at day 1 before the first IP dosing, days 3, 7, 14* and E.D. For day 14, an aliquot of urine will be taken from the 24 hour urine collection taken for urinary delamanid metabolites.
Urinary Delamanid Metabolites				X				X				A 24 hour urinary sample will be taken at the following timepoints for participants in a dosing arm containing delamanid: Day 1 from time of IP dose until prior to IP dose on Day 2, and on Day 14 from time of IP dose until 24 hours later.

Procedure	Screening			Intervention Period					Follow-Up		Notes
	Visit										E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
Point of Care Blood Glucose		X						X				Point of care blood glucose or HbA1C test to coincide with the day of the FDG-PET/CT scan and does not have to be repeated on the other days. Not needed in participants that are not undergoing FDG-PET/CT scanning.
PK Sampling												

PK Blood Sampling								X*			X	A single pre-dose PK sample will be collected on Day 14 followed by three PK samples at times 1 hr, 2 hr and 3-6 hrs post-dose. A single blood sample will be collected at the 3-6 hr time point. With the exception of BTZ-043. *For BTZ-043 PK blood samples should be taken on Day 14 at 0.0h (within 90 mins pre-dose) and post-dose at 15min, 30min, 1.0h, 1.5h, 2.0h, 3.0h, 4.0h, 6.0h, 8.0h, 10.0h, 12.0h, 24.0h (pre-dose the following day). Time window: 0h – 2h (± 5 min), 3h – 24h (± 10 min). For the arms that do not include BTZ-043, sample to be taken within 30 minutes prior to the administration of the dose on Day 14. For the rest of the PK time points, samples to be taken within ±10 minutes from the nominal time point (allowable window). At E.D a PK sample will be taken before the time of the planned daily dosing. If this is not possible, a spontaneous PK sample will be taken. All values are relative to the time of day that the study treatment is administered on Day 14. PK sampling is only to be performed on participants receiving GSK3036656,BTZ-043, bedaquiline,delamanid, pretomanid, moxifloxacin and linezolid but not standard of care.
PK Microsampling								X			X	The same regimen of sparse PK sampling will also be adopted for the experimental blood microsampling, for participants assigned to a treatment arm containing GSK3036656. NOTE: Microsampling will not be conducted for the arms added under protocol amendment 3 (GSK3036656 + linezolid, GSK3036656 + pretomanid and GSK3036656 + moxifloxacin).

Procedure	Screening			Intervention Period						Follow-Up		Notes
	Visit											E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
AE/SAE/Concomitant Medications												
AE Review				←=======X=======→								Adverse events (AE) will be collected by the Investigator from the time a participant receives his/her first dose of IP through to the Visit 19 (day 28) Follow up Visit
Serious Adverse Event Review	X	X	X	←=======X=======→								Serious Adverse Events will be collected by the Investigator from the time a participant signs the Informed Consent.
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	

Procedure	Screening			Intervention Period						Follow-Up	Notes
	Visit										E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
Sputum Sampling												
Spot sputum	X		X	X	X Day 3 & 7				X		X	Sputum samples for sputum smear microscopy, molecular rapid test and GeneXpert (confirmation of Mycobacterium tuberculosis and rifampicin susceptibility). If the first spot sputum or overnight sputum sample shows an unfavourable result, the tests may be repeated on a freshly collected spot sputum or overnight sputum sample and that result used instead. RS ratio and TB-MBLA and READ-TB biomarkers (spot sputum), on sputum collected at Day -1 or Day 1 before the first IP dosing, then days 3, 7, 15 and E.D. Two spot sputum samples to be collected for biomarkers. Refer to TASK Laboratory Manual for processing information.

Overnight sputum	X	X	X	X	X	X	X	X				Overnight sputum sampling may start at Screening visit (day -9 to -3) or on Visit 2 (day –2) and will continue daily until Visit 7 (day 4). Additional sampling will be conducted at visit 9 (day 6), Visit 11 (day 8), Visit 13 (day 10), Visit 15 (day 12) and Visit 17 (day 14). Sputum sampling will stop on the morning of Visit 18 (day 15). Sputum collection will start in the afternoons and continue for approximately 16 hours overnight. The 16-hour sputum sampling for each of the sampling days must be finished prior to the administration of the next day's IP. Overnight sputum collection may be collected as many times as required over the screening period until an eligible sample is obtained. Of the pre-treatment period samples collected, only the Visit 2 (day-2) and Visit 3(day -1) overnight sputum samples will be used for the efficacy endpoint tests. The day sputum collection starts reflects the day to which that sample applies. e.g. a sample whose collection starts on day 1 and ends on day 2 is designated as the day 1 overnight sputum sample (and results). Minimum inhibitory concentration (MIC) and speciation of the infecting organism by polymerase chain reaction (PCR) will be estimated for all treatment arms from a culture collected on a pre-treatment day (day-1 or day-2) and from the last available culture on a treatment day (day 14 or earlier, but not earlier than day 8). Drug susceptibility testing of M. tuberculosis for sensitivity to rifampicin with a molecular method will be tested at Visit 1. Susceptibility to INH, Rif, EMB and PZA will be tested on a culture grown from a baseline sample (day -2 or day -1).

Procedure	Screening			Intervention Period					Follow-Up		Notes
	Visit										E.D = early discontinuation/withdrawal
	1	2	3	4	5 to 10	11	12 to 16	17	18	19	E.D	The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible
	Day											
	(-9 to -3)	-2	-1	1	2-7	8	9-13	14	15	28± 7		All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.
												READ-TB and PATHFAST LAM biomarkers (overnight sputum) on sputum collected at Day -1, days 3, 7, 14. Where days coincide, the same overnight sputum samples collected for EBA analyses will be used for analyses of these 2 biomarkers. i.e. Day -2 overnight sputum sample will be used for Day -1 biomarker sample, Day 2 overnight sputum sample will be used for Day 3 biomarker sample and Day 6 overnight sputum sample will be used for the Day 7 biomarker sample. Day 14 overnight sputum will be used for the Day 15 biomarker sample.

2. INTRODUCTION

GSK3036656 is a compound under development with a novel mechanism of action for the treatment of tuberculosis (TB). It suppresses protein synthesis in *Mycobacterium tuberculosis* (Mtb) by selectively inhibiting the enzyme Leucyl t-RNA synthetase and is currently under investigation in a monotherapy 14 day early bactericidal activity (EBA) study.

2.1. Study Rationale

With drug-resistance becoming increasingly prevalent for TB, all-new drug combinations that avoid existing resistance are urgently needed. The Click-TB consortium, funded by the European Union, are performing a series of dual combination EBA studies. GSK3036656 will be included in this series. The studies will incorporate novel radiological, immunological and molecular TB biomarkers to complement traditional sputum microbiological readouts.

While the monotherapy study will have established proof-of-principle of antituberculosis activity of GSK3036656, this will be the first study where GSK3036656 is dosed in combination with other TB drugs, including the new drug candidate BTZ-043. The study will provide safety and tolerability data that will inform future combination studies with GSK3036656. EBA studies have been considered a fundamental component of the early assessment of anti-tuberculosis drugs in man. Nonetheless, there may be potential to improve the predictivity of an EBA to longer term relapse outcomes. Combining the EBA readout with immunological and radiological biomarkers may enable this. The data from this study will also be integrated with that from other studies; a statistical model will be developed combining microbiological and biomarker readouts of all dual combination EBA studies within Click-TB with the intent of better predicting future long-term pivotal outcomes and to understand the contribution of each single drug in its respective combinations. The model will then rank the drug combinations with the greatest benefit:risk profile from which those with potential safety concerns will be removed. The most promising regimens will be taken forward into a longer study, with the aim of identifying a novel regimen for TB in addition to validating the statistical model outside of the Click-TB Consortium.

2.2. Background

Tuberculosis remains a concerning health problem, with Mtb now causing more deaths than human immunodeficiency virus (HIV)/ Acquired Immune Deficiency Syndrome (AIDS). In 2020, 1.5 million people died from TB, making it the leading bacterial infectious disease killer in the world [World Health Organization (WHO), 2021 Report]. The current long-standing first-line antituberculosis agents are relatively ineffective in controlling the TB epidemic in high-burden countries. Treatment takes 6-9 months to complete and is associated with side effects resulting in poor compliance which leads to treatment failure and an increased likelihood of developing drug-resistance.

Drug-resistant TB poses a major threat to control of the TB epidemic. The prevalence of multi drug-resistant TB (MDR: resistance to at least isoniazid and rifampicin) and

extensively drug-resistant (XDR: MDR plus resistance to at least a fluoroquinolone and either/both bedaquiline and linezolid) continues to increase. The WHO estimates that 3% of new and 18% of previously treated TB cases occurring worldwide in 2019 had MDR-TB, which translates into close to half a million new cases of MDR-TB [Mirzajev, 2021].

The treatment of DR-TB remains sub-optimal due to constraints such as availability of drugs, duration (6−24 months), and significant toxicities leading to poor compliance and an increased risk of developing further drug-resistance. The new 6-month Bedaquiline Pretomanid Linezolid (BPaL) regimen or the 9-12 month shorter course regimen for MDR-TB recently proposed by the WHO is optimising the use of currently known substances but only a minority of MDR cases are likely to qualify for it [WHO, 2021].Despite the lengthy duration, DR-TB treatment is only successful in approximately 70% of cases, further escalating the threat to global health [WHO, 2021].

The development of new drug combinations that are effective against drug-resistant strains of Mtb, and that have the potential to shorten the duration of TB treatments offers the hope of tackling the TB pandemic. The addition of promising new drugs such as moxifloxacin, bedaquiline [Rustomjee, 2008; Diacon, 2009; Diacon, 2013], delamanid [Diacon, 2011b], pretomanid [Diacon, 2010; Diacon, 2012], and new oxazolidinone candidates [Wallis, 2014; Furin, 2016] for M/XDR-TB is an important step in that direction. However, questions remain related to their best possible use in combination regimens.

A new treatment regimen requires at least 3 different drugs to which no clinical resistance exists. However, potential antagonism in humans between drugs [Mdluli, 2009], for instance pretomanid and bedaquiline, and the additive potential for significant toxicity e.g. QTc prolongation of moxifloxacin [Bloomfield, 2008], bedaquiline [Matteelli, 2010], limit the number of possible combinations. This highlights the need for the development of additional new chemical entities that strike an appropriate balance between antituberculosis activity and safety profiles, a balance that will enable new future drug combinations that make the optimal use of previously-developed entities.

GSK3036656 is a compound with a novel mechanism of action under development for the treatment of TB. It suppresses protein synthesis in Mtb by selectively inhibiting the enzyme Leucyl t-RNA synthetase.

There is no known circulating resistance to GSK3036656, and GSK3036656 is active against both drug-sensitive and drug-resistant strains of Mtb when screened in a variety of in vitro and in vivo animal models. The MIC is low (MIC90 of 0.16 µM against a panel of clinical isolates) and the drug shows potent activity in animal models, resulting in very low predicted efficacious human doses. In vitro data show that the risk of drug-drug interactions with GSK3036656, either as perpetrator or victim, is low. These factors make GSK3036656 an attractive potential candidate for the treatment of tuberculosis.

A description of the chemistry, nonclinical and clinical data generated to date for GSK3036656 is provided in the Investigator's Brochure (IB).

BTZ-043, belonging to the chemical class of benzothiazinones, is a new antimicrobial for the treatment of tuberculosis. Its mechanism of action is based on the covalent inhibition

of a key enzyme involved in mycobacterial cell wall synthesis. In mycobacteria the nitro substituent of BTZ-043 is reduced to a transient nitroso moiety, which then reacts with an essential cysteine residue in the enzyme decaprenylphosphoryl-ß-D-ribose-2'-epimerase (DprE1). DprE1 itself is required for the biosynthesis of decaprenylphosphoryl-β-D-arabinose, an essential component for the cell wall assembly of mycobacteria. BTZ-043 is highly selective for Mycobacteria species (and some other members of Actinomycetales), without affecting the gut flora.

BTZ-043 preclinical evaluation has been extensive for a compound at this development stage. The drug showed substantial activitywith a good safety profile.

So far, the drug has been given to humans in a phase 1a single ascending dose study, a seamless phase 1B/2A study in TB patients, and a human ADME study. Overall, 96 persons have received BTZ-043 to date, there were no safety concerns and the drug showed excellent anti-mycobacterial activity, comparable to rifampicin 10 mg/kg in other studies.

A description of the chemistry, nonclinical and clinical data generated to date for BTZ-043 is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Risks of clinical significance along with mitigation strategies are summarised in Table 1

Table 1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) GSK3036656		
Reduction in red blood cell count	**Non-Clinical** In a 4-week rat study (doses 3, 10 & 30 /kg/d) - dose-dependent decline in reticulocytes (by up to 52% in males and 62% in females) at day 7 followed by normal levels by day 14 and increased levels by day 29/30 compared to controls. Hgb levels decreased by 10-13% compared to controls on day 14 and day 29/30. In a 4 week dog study (doses 5, 10 & 20 mg/kg/d) - mild dose-dependent decrease in Hgb on day 14 (by about 10% compared to controls) with recovery by week 4. Reticulocyte counts unaffected. Dogs not bled on day 7. No histopathological changes in bone marrow or other relevant histopathology in the 4-week studies.	Standard safety haematology and clinical chemistry assessments will be performed and both trends and changes outside normal range will be monitored as part of laboratory safety assessments. Participants whose haemoglobin drops below pre-specified limits will be withdrawn from study intervention (Section 7.1.3). Patients with a confirmed haemoglobin <8.0g/dL after randomisation will require enhanced observations, with a repeat haemoglobin level and discussion of patient status with the GSK medical monitor.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical In the 201040 study, a possible trend of decreased haemoglobin from baseline to follow-up was noted in aggregate haematology data. The mean change from baseline to follow-up was -4.9 g/L in the 15 mg repeat dose cohort, compared to -1.5 g/L in the placebo group. None of the values hit potential clinical importance (PCI) criteria, and declines were not clinically relevant. No clinically significant trends in reticulocyte values were observed, and there were no values of potential clinical importance reported for reticulocytes.	
Reduction in white blood cell count	**Non-Clinical** In the 4-week rat study, decrease of up to 37% in total leucocyte count on day 29/30 compared to controls. In the 4-week dog study, no reported effects on white blood cells. **Clinical** No clinically significant trends in leukocyte or neutrophil count values were observed. Two subjects showed PCI values. One subject had low neutrophil count (normal range 1.57-6.81 ×	White blood cell count will be monitored as part of laboratory safety assessments. Any clinically significant changes will be followed up until levels are not clinically significant. Participants developing neutrophil counts <500/mm3 (0.5x109/L) will be withdrawn from the study (Section 7.1.3).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	10^9/L) from screening (1.38) until follow-up (1.41), and also showed low leukocyte count (normal range 3.3-9.8 × 10^9/L) on Day 4 (2.5), Day 10 (2.6) and Day 14 (2.9) and was within normal range at follow-up. Given the low screening values, this observation was considered likely related to the subject's Black or African American race. A second subject had a single low neutrophil count at follow-up (1.48).	
Heart valvular and vascular pathology	**Non-Clinical** In a 7-day dog dose range finding (DRF) study – minimal focal subendocardial hemorrhage on the atrial surface of the left atrioventricular valve observed in both animals at the top dose of 60 mg/kg/d. In a 10-day dog investigative study at 65 mg/kg/d – vascular lesions (including minimal focal necrosis and inflammatory infiltrate) in 3 out of 8 dogs. In the 4-week dog GLP study - no heart or valve changes were observed up to the top dose of 20 mg/kg/day and there was no increase in inflammatory markers.	Valvular pathology can bemonitored in humans with non invasive echocardiography, these will be performed at screening and day 14 or early withdrawal. Vascular pathology is not readily monitorable in humans, To avoid risk to study participants, dosing will be limited to doses at which individual exposures do not exceed AUC0-24 and Cmax to 15 µg.hr/mL and 1.5 µg/mL, respectively. These exposures are 10-fold below the lowest NOAEL achieved in the 17 week studies (rat)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In the 17 week GLP dog study there were no heart or valve changes up to the top dose of 45 mg/kg/day. In the 17 week rat study there were no changes in cardiac pathology up to the top dose of 30 mg/kg/day. Valvular or vascular pathology were not observed in rats. This pathological change is not commonly seen in animals, and its mechanism and significance to humans are not clear. A correlation between the presence of hemodynamic changes and the presence of this pathology is suspected, but currently unproven. **Clinical** Echocardiograms were performed at screening and follow up in the 201040 First Time-In Human (FTIH) study in order to exclude participants with pre-existing valve or other cardiac abnormalities from the study, and to detect the presence of abnormalities after completion of the study. No abnormalities were detected. No SAEs, or AEs of cardiovascular nature were reported. There was no change from baseline in heart rate observed at any dose. No trends in blood pressure change were observed.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Cardiac telemetry and echocardiogram-related interpretations were within normal range. There were no clinically significant ECG observations. There were no troponin I abnormalities in participants after receiving study drug.	
Hemodynamic changes	**Non-Clinical** Hemodynamic changes in several studies at ≥100 mg/kg in rats and ≥20 mg/kg in dogs - increased heart rate (rats and dogs), increased (rats) or decreased (dogs) blood pressure. **Clinical** Data from the 201040 FTIH study showed no significant changes in vital signs assessments during the study, and no clinically significant changes in ECG or telemetry assessments including QTc and PR intervals.	Vital signs monitoring will be implemented in this study.
GSK3036656 is cleared through the kidneys	The main route of clearance for GSK3036656 is renal and there is therefore a risk that participants with low creatinine clearance may accumulate GSK3036656 and exceed predefined exposure limits.	Participants with an estimated creatinine clearance less than 75 mL/min will be excluded.
Skin depigmentation	**Non-Clinical** In a 17 week dog toxicology study (doses 0, 6, 20 & 45 mg/kg /day): loss of pigmentation on	The duration of dosing in this study (14 days) is shorter than that used in the dog toxicology study and the maximum exposure (AUC0-24) has been capped at 15 ug.h/mL (10-fold below

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	the eyelids, nose or muzzle of all animals at 45 mg/kg/day group (week 17 AUC0–t mean 405 µg.h/mL) and most animals in the 20 mg/kg/day group (week 17 AUC0–t 176 µg.h/mL). PNL-2 (a melanocyte marker) immunohistochemistry staining demonstrated moderate cytoplasmic positivity in a population of cells in the basal region of the epidermis (interpreted to be melanocytes). The decreased pigmentation was therefore not associated with a loss of melanocytes in affected animals on immunohistochemistry. Depigmentation was not observed in the 0 or 6 mg/kg/day group (59.4 ug/h/mL). Depigmentation was not observed in the 2 previous 4 week dog toxicology studies up to 45 mg/kg/day (week 4 AUC0-t. 388 ug.h/mL). **Clinical** No adverse events were reported in the 201040 FTIH study that would be considered consistent with depigmentation.	effect level for loss of pigment in the 17 week dog study). The physical examination of study participants will include visual examination of the skin. Participants with vitiligo will be excluded from the study to avoid confounding skin assessment at baseline and follow-up physical examinations.
Teratogenicity of GSK3036656	**Non-clinical safety** Results from the definitive rat embryo-fetal toxicology are as follows: **60 mg/kg/day**: Reductions in fetal viability and reduced fetal weights, with minimal reductions in body weight gains and visceral and skeletal	Only include women of childbearing potential who agree to the use of a highly effective contraceptive method combined with abstinence during the inpatient portion of the study and male partner use of a condom until after the follow-up visit.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	malformations including ventricular septal defects (13 animals across 8 litters) and cleft palates (10 animals/6 litters), extra vertebrae and ribs. **20 mg/kg/day**: Reduced fetal weights and incidences of ventricular septal defects (2 animals across 2 litters) that were outside the historical control data in the absence of any maternal effects. Visceral and skeletal malformations and variations observed. **6 mg/kg/day**: skeletal malformations and variations (supernumerary vertebrae and ribs) **2 mg/kg/day**: No effect level	Only include women of childbearing potential with a negative high sensitivity pregnancy (urine or serum) at screening and just before the first dose. Perform pregnancy tests at screening, just prior to the first dose on day 1, and at study days 3 or 4 and 8. Prior to discharge on day 15 and again at follow-up. The risk of teratogenicity is clearly described in the informed consent along with the measures necessary to prevent a pregnancy exposure to the study drug.
Study Procedures		
Participants exposed to ionising radiation as a consequence of participation in this study.	The ionising radiation exposure comes from the administered radioligand (FDG), a high resolution CT (HRCT) for anatomical localization and low dose CT scans performed in order to correct the PET data for tissue attenuation. The maximum effective dose of ionising radiation that subjects in this study may be exposed to is 21.7 mSv. This is equivalent to approximately 9 times the worldwide average yearly exposure (2.4 mSv) from natural background radiation.	The study has been designed to keep the radiation dose as low as reasonably practicable (ALARP) whilst obtaining images of sufficient quality to meet the objectives. To avoid recruitment of radiation worker or serial study volunteers, participants who have been estimated to have been exposed to ionising radiation in excess of 10mSv above background over the previous three year period as a result of occupational exposure to radiation or as a result of research studies are

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	The additional risk of developing a fatal malignancy as a result of these exposures has been estimated as approximately 1 in 900 for the whole adult population, assuming normal health and life expectancy. The anticipated lower age range of the patient population to be studied may result in an increased risk but this must be balanced against their reduced life expectancy which may lower the lifetime risk for these individuals. The level of risk may therefore be assumed to broadly fall within the ICRP 62 intermediate Category IIb, where the benefit should be more directly aimed at the cure or prevention of disease.	excluded. Clinically justified (therapeutic or diagnostic) exposures are not included in the exposure calculation. Participants are asked about any occupational exposure or previous participation in research studies at screening so that dose estimates can be obtained where necessary. Details of the maximal dose of ionising radiation that participants in this study may be exposed to are given in Section 10.6. To minimise the number of participants exposed to PET/CT, only participants who are 25 years of age or older and females of non-childbearing potential will be eligible for PET-CT scan assessment, recognising that the risk from medical radiation exposure is higher in younger age groups.
Other Interventions Delamanid♦		
Cardiovascular toxicity**	QT prolongation has been observed (more common with hypoalbuminaemia) in patients treated with delamanid. This prolongation increases slowly over time in the first 6 to 10 weeks of treatment and remains stable thereafter.	Due to 14 days dosing, the risk of QT prolongation in study participants is small. Exclusion criteria have been added to exclude participants with QTc interval>450Msec (see Section 5.2). ECG will be done at baseline and will be monitored throughout the study at the timepoints listed in Section 1.3.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Stopping rules for have been implemented as described in Section 7.2.
Hepatotoxicity* *	Elevations in transaminases have been observed in patients taking delamanid.	Exclusion criteria have been added to exclude participants with elevated ALT (see Section 5.2). Liver enzymes will be monitored throughout the study at the timepoints listed in Section 1.3. Stopping rules for liver chemistry have been implemented as described in Section 7.1.1.
Haematological effects*	Leucopenia, anemia, thrombocytopenia were observed in patients taking delamanid in the clinical study.	Regular monitoring throughout the study at the timepoints listed in Section 1.3. Stopping criteria for haemoglobin and neutrophil count have been implemented as described in Section 7.1.3.
Psychiatric events	Psychotic disorder, agitation, aggression, depression were reported in clinical study.	Routine monitoring by the investigative staff
GI tolerability/ toxicity	Abdominal pain, diarrhoea, nausea and vomiting were reported as very common adverse event.	Routine monitoring by the investigative staff

Other Interventions Bedaquiline1 ♦		
Cardiovascular toxicity** Bedaquiline prolongs the QTc interval. In clinical study, mean increase in QTc was observed in bedaquiline from week 1.	Bedaquiline prolongs the QTc. In the clinical study, mean increase in QTc was observed from week 1 in patients receiving bedaquiline in the clinical study.	Due to 14 days dosing, the risk of QT prolongation in study participants is small. Exclusion criteria have been added to exclude participants with QTc interval>450Msec (see Section 5.2) ECG will be done at baseline and will be monitored throughout the study at the timepoints listed in Section 1.3. Stopping rules for have been implemented as described in Section 7.1.2.
Hepatotoxicity**	In clinical study, hepatic ADRs developed more in bedaquiline treated patients than those treated with other drugs used to treat TB.	Exclusion criteria have been added to exclude participants with elevated ALT (see Section 5.2). Liver enzymes will be monitored throughout the study at the timepoints listed in Section 1.3. Stopping rules for liver chemistry have been implemented as described in Section 7.1.1.
Other Interventions BTZ-043♦		
Reduction in red blood cell count	**Non-Clinical** In a repeated dose oral toxicity study performed in minipigs, the consistent toxicological finding of marginal effects on red blood cell paramenters (red blood cell count, haemoglobin concentration and haematocrit)	Standard safety haematology and clinical chemistry assessments will be performed and both trends and changes outside normal range will be monitored as part of laboratory safety assessments.

	was observed on Day 14 with evidence of recovery at the end of treatment. **Clinical** No clinically significant trends in reticulocyte or red blood count values have been observed in human studies.	Participants whose haemoglobin drops below pre-specified limits will be withdrawn from study intervention (Section 7.1.3). Patients with a confirmed haemoglobin <8.0g/dL after randomisation will require enhanced observations, with a repeat haemoglobin level and discussion of patient status with the BTZ-043 medical monitor.
Neurological findings	**Non-Clinical** In a 6-month toxicity study performed in Wistar rats, doses of 60, 130 and 380 mg/kg bw/day, were administered. **380 mg/kg/day** : piloerection, hunched back, decreased activity and ataxia were observed at minimal severity and with decreasing incidence during the course of the study. Recumbency was only occasionally observed. These findings were transient and were resolved before the next treatment at the latest from Week 5 onwards. **Clinical** Mild dizziness has been observed. In addition, a case of mild peripheral neuropathy has been observed. The onset of symptoms after only 4 doses of BTZ-043 make a drug-induced neuropathy seem very unlikely, albeit not impossible. Thus, the investigator classified the peripheral neuropathy as “possibly related” to BTZ-043.	The investigative staff will document any neurological findings as part of standard adverse event reporting.

Hepatic toxicity/findings	**Non-clinical** In a 28-day subacute toxicity study performed in Wistar rats, doses of 60, 170 and 470 mg/kg were administered daily by oral galvage. **170 mg/kg:** mean liver weights at necropsy were increased by 12% for body weight relative values in female rats. **470 mg/kg:** mean liver weights at necropsy were increased over control mean (by 38% and 15% for body weight relative value, in females and males, respectively). Following a 28-day recovery period, the mean liver weights were comparable to the control mean in males and were slightly higher in females (by approximately 16% for body weight relative values). AST and ALT activity was slightly higher in females on day 29. **Clinical** In the clinical phase Ib/IIa study, 1 patient experienced a moderate increase in ALT (BTZ-043 1750 mg), and 6 patients experienced mild increases in AST and/or ALT of at least 2x ULN (3 Patients on 250 mg BTZ-043, 2 on 1000 mg, 1 on 1250 mg). All these started to decline again despite continued dosing with BTZ-043, so are classified as signs of adaptation of hepatic metabolism, rather than hepatic toxicity.	Exclusion criteria have been added to exclude participants with elevated ALT (see Section 5.2). Liver enzymes will be monitored throughout the study at the timepoints listed in Section 1.3. Stopping rules for liver chemistry have been implemented as described in Section 7.1.1.

Hemodynamic changes	**Clinical** In the Phase Ia study, a slight and transient increase in mean systolic blood pressure was observed after administration of 250 and 500 mg BTZ-043. The maximal effect was observed at 0.5 and 1 hours after dosing (+10.0 and +12.1 mmHg, respectively compared to pre-dose). A slight increase in heart rate was observed after doses of 500 mg (increase of 7.2 and 11.0 bpm at 0.5 and 1.0 hour post-dose). No hemodynamic changes and cardiovascular safety signals have been observed in the hAME study and in the recently completed phase Ib/IIa study.	Vital signs monitoring will be implemented in this study.
Gastrointestinal findings	**Non-Clinical** In a toxicity study performed in minipigs, necropsy revealed hyperkeratosis of the fundic region and erosions. In a 28-day subacute toxicity study performed in Wistar rats, at 470 mg/kg, necropsy revealed a dilated stomach, and both stomach and intestines were filled with digestive contents suggestive of slow digestion and delay in gastric emptying time after treatment. **Clinical** In the phase Ib/IIa study, nausea was observed 12 times (11 times in participants receiving BTZ-043)	The investigative staff will document any gastrointestinal findings as part of standard adverse event reporting.

BTZ-043 is cleared through the kidneys	The main route of clearance for BTZ-043 is renal and there is therefore a risk that participants with low creatinine clearance may accumulate BTZ-043 and exceed predefined exposure limits.	Participants with an estimated creatinine clearance less than 90 mL/min will be excluded.
Other Interventions Pretomanid Safety and effectiveness of pretomanid have not been established for its use in combination with medicinal products other than bedaquiline and linezolid as part of the recommended dosing regimen		
Hepatotoxicity	Hepatotoxicity may occur with use of the regimen consisting of pretomanid, bedaquiline and linezolid. Modification or interruption of linezolid dosing may be needed during the course of therapy to manage the known linezolid toxicities. In the STAND [Tweed CD, Wills GH, Crook AM, et al.] trial increased hepatotoxicity was observed in RS-TB participants randomised to the experimental arms containing pretomanid, moxifloxacin and pyrazinamide when compared to standard HRZE arm (noting that pyrazinamide which contributes to hepatotoxicity was given for 4 or 6 months in the experimental arms and 2 months in the control).	Pretomanid will not be combined with pyrazinamide in this EBA. Subjects with impaired LFT are noteligible for the study (alanine aminotransferase (ALT) grade 2 (≥2.0 × ULN); serum total bilirubin >1.5xULN) (See Section 5.2) Regular LFT and clinical examination for abdominal symptoms are a part of the safety monitoring Current alcohol or drug abuse sufficient to compromise the safety or cooperation of the participant is an Exclusion Criteria (See Section 5.2) Liver Chemistry Stopping Criteria are stipulated in Section 7.1.1
Peripheral neuropathy and optic neuropathy Δ	Peripheral neuropathy associated with linezolid is generally reversible or improved with interruption, dose reduction, or discontinuation of linezolid dosing.	Subjects with pre-existing cataract and retinopathies will be excluded from the study. Visual acuity and colour vision (e.g. Ishihara plate testing) will be performed at screening.

	Optic neuropathy is a known adverse reaction of linezolid. Two patients (2%, common) in the Nix-TB trial developed optic neuropathy, both after 16 weeks of treatment. Both were serious, confirmed on retinal examination as optic neuropathy/neuritis, and resulted in discontinuation of linezolid; both adverse reactions resolved.	For participants reporting any ophthalmological adverse events, referral for ophthalmologist examination (including slit lamp, fundoscopy, and measurement of intraocular pressure) will be made for participants reporting any visual impairment during the study. Exclusion criteria have been added to exclude diabetic participants that do not have eye screening results during the last 12 months (see Section 5.2)
Myelosuppression	Myelosupression is more common in subjects on the combination with linezolid. Haematologic parameters are variable from measurement to measurement, and decreases should be evaluated in the context of the patient's overall medical condition	Standard safety haematology and clinical chemistry assessments will be performed and both trends and changes outside normal range will be monitored as part of laboratory safety assessments. Participants whose haemoglobin drops below pre-specified limits will be withdrawn from study intervention (Section 7.1.3). Participants developing neutrophil counts <500/mm3 (0.5x109/L) will be withdrawn from the study (Section 7.1.3).
QT prolongation	QT prolongation is a known adverse reaction of bedaquiline. Bedaquiline in combination with pretomanid appears to result in a higher QT prolongation than expected with bedaquiline alone. However, the impact of pretomanid has not been fully characterized.	QTcF prolongation is an Adverse Event of Special Interest (AESI) Exclusion criteria have been added to exclude participants with QTcF > 450 msec (See Section 5.2)

	The QT prolongation risk for the combination regimen has not been established at exposures higher than therapeutic levels. The risk may be increased if the systemic exposure of pretomanid is elevated A thorough QT study (in healthy volunteers) for pretomanid showed no clinically meaningful increase in QTc after single doses of 400 mg and 1000 mg of pretomanid. Pretomanid was found to have low risk to prolong the QTc at therapeutic exposures.	Exclusion Criteria have been added to exclude participants withCardiovascular disease such as myocardial infarction, heart failure, coronary heart disease, clinically significant arrhythmia, tachyarrhythmia, or pulmonary hypertension (Section 5.2) Exclusion Criteria have been added to exclude participants with long QT syndrome or family history of long QT syndrome or sudden death of unknown or cardiac-related cause. (Section 5.2) Regular ECG, serum potassium, calcium, and magnesium are part of safety monitoring (Section 10.2) QTc Stopping criteria have been implemented as described in Section 7.1.2)
Other Interventions Moxifloxacin		
Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions	Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. In the analysis of ECGs obtained in the clinical trial program, QTc prolongation with moxifloxacin was 6 msec ± 26 msec, 1.4% compared to baseline. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may	QT prolongation is an AESI Exclusion criteria have been added to exclude participants with QTcF > 450 msec (Section 5.2) Exclusion Criteria have been added to exclude participants with: Cardiovascular disease such as myocardial infarction, heart failure, coronary heart disease, clinically significant arrhythmia,

	also be more susceptible to drug-associated effects on the QT interval. Medication that can reduce potassium levels should be used with caution in patients receiving moxifloxacin. Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia. Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions The magnitude of QTcF prolongation may increase with increasing concentrations of the drug.	tachyarrhythmia, or pulmonary hypertension (Section 5.2) Exclusion Criteria have been added to exclude participants with: Long QT syndrome or family history of long QT syndrome or sudden death of unknown or cardiac-related cause (Section 5.2) Regular ECG, serum potassium, calcium, and magnesium are part of safety monitoring (Section 10.2) QTc stopping criteria have been implemented as described in Section 7.1.2)
Hepatotoxicity	Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin.	Subjects with impaired LFT are not eligible for the study (alanine aminotransferase (ALT) grade 2 (≥2.0 × ULN); serum total bilirubin >1.5xULN) (See Section 5.2) Regular LFT and clinical examination for abdominal symptoms are a part of the safety monitoring (Section 10.2) Current alcohol or drug abuse sufficient to compromise the safety or cooperation of the participant is an Exclusion Criteria (See Section 5.2) Liver Chemistry Stopping Criteria are stipulated in Section 7.1.1

Hypersensitivity / allergic reactions	Hypersensitivity and allergic reactions (including anaphylactic reactions) have been reported for fluoroquinolones including moxifloxacin after first administration.	Dosing by the trained staff, followed by the clear supervision Investigator sites appropriately equipped for providing emergency care
Tendon rupture, tendon inflammation	Tendon inflammation and rupture may occur with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids.	Careful clinical monitoring
Vision disorders	Uncommon: visual disturbances including diplopia and blurred vision (especially in the course of CNS. Very rare: transient loss of vision (especially in the course of CNS reactions)	Subjects with pre-existing cataract and retinopathies will be excluded from the study. Visual acuity and colour vision (e.g. Ishihara plate testing) will be performed at screening. For participants reporting any ophthalmological adverse events, referral for ophthalmologist examination (including slit lamp, fundoscopy, and measurement of intraocular pressure) will be made for participants reporting any visual impairment during the study. Exclusion criteria have been added to exclude diabetic participants that do not have eye screening results during the last 12 months (see Section 5.2)
Peripheral neuropathy Δ	Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness	Careful clinical monitoring
Psychiatric reactions	Psychiatric reactions may occur even after the first administration of quinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal	Careful clinical monitoring

	thoughts and self-endangering behaviour such as suicide attempts with history of psychiatric disease	
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, localized or general abdominal pain, constipation, dyspepsia are common AEs. Clostridioides difficile associated diarrhea should be considered in subjects with diarrhoea on moxifloxacin	Carefull clinical monitoring, stool investigation for Clostridioides difficile toxin PCR, clinician may start empirical treatment with oral vancomycin as per local guidance.
Hypoglycemia	Postmarketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents and taking moxifloxacin	Blood glucose is in the list of regular safety laboratory tests. Diabetic participants receiving moxifloxacin will be informed to monitor their blood sugar levels more closely.
Other Interventions Linezolid		
Myelosuppression	Myelosuppression (including anaemia, leukopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. This can be severe and life threatening. These adverse effects were on some occasions reversible with lowering the dose of drug. Haematological toxicities are less common with current strategies of once-daily dosing.	Standard safety haematology and clinical chemistry assessments will be performed and both trends and changes outside normal range will be monitored as part of laboratory safety assessments. (Section 10.2) Participants whose haemoglobin drops below pre-specified limits will be withdrawn from study intervention as described in Section 7.1.3. Participants developing neutrophil counts <500/mm3 (0.5x109/L) will be withdrawn from the study as described in Section 7.1.3.

Lactic acidosis	Patients who develop recurrent nausea or vomiting should receive immediate medical evaluation, including evaluation of bicarbonate and lactic acid levels, and interruption of linezolid should be considered	Careful clinical and laboratory monitoring
Serotonin syndrome	There have been spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs). Therefore, linezolid and serotonergic agents, such as serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), should not usually be co-administered, except where administration of linezolid and concomitant serotonergic agents is essential. In those cases patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination.	Careful clinical monitoring, vital signs monitoring. Serotonergic agents should not be co-administered with linezolid unless their coadministration is essential. If serotonin syndrome occurs linezolid will be stopped immediately.
Peripheral and optic neuropathy Δ	Peripheral neuropathy, as well as optic neuropathy and optic neuritis, sometimes progressing to loss of vision, have been reported in patients treated with linezolid; these reports have primarily been in patients treated for longer than 28 days.	Careful clinical monitoring Subjects with pre-existing cataract and retinopathies will be excluded from the study. Visual acuity and colour vision (e.g. Ishihara plate testing) will be performed at screening. For participants reporting any ophthalmological adverse events, referral for ophthalmologist examination (including slit lamp, fundoscopy, and measurement of intraocular pressure) will

		be made for participants reporting any visual impairment during the study. Exclsuion criteria have been added to exclude diabetic participants that do not have eye screening results during the last 12 months (see Section 5.2).
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, localized or general abdominal pain, constipation, dyspepsia are common AEs. *Clostridioides difficile* associated diarrhea should be considered in subjects with diarrhoea on Linezolid	Carefull clinical monitoring, stool investigation for *Clostridioides difficile* toxin PCR, clinician may start empirical treatment with oral vancomycin as per local guidance.
Hepatotoxicity	Abnormal liver function test; increased AST, ALT or alkaline phosphatase are common AEs in subjects on Linezolid	Subjects with impaired LFT are not eligible for the study (alanine aminotransferase (ALT) grade 2 (≥2.0 × ULN); serum total bilirubin >1.5xULN) (See Section 5.2) Regular LFT and clinical examination for abdominal symptoms are a part of the safety monitoring Current alcohol or drug abuse sufficient to compromise the safety or cooperation of the participant is an Exclusion Criteria (Section 5.2) Liver Chemistry Stopping Criteria are stipulated in Section 7.1.1.

* Potential for synergistic or additive effects when GSK3036656 is co-administered with delamanid. Caution recommended

* * Potential for synergistic or additive effects when co-administering bedaquiline with delamanid. Caution recommended

[1]Refer to bedaquiline with delamanid prescribing information for full benefit-risk profile.

Adverse drug reactions (ADRs) reported from the uncontrolled and controlled phase 3 trials treated with pretomanid in combination with bedaquiline and linezolid are summarized in the table above. ADRs considered attributed to linezolid are marked with Δ. Refer to the Summary of Product Characteristics of bedaquiline and linezolid for more information on adverse reactions caused by these 2 medicinal products.

♦ Risks relating to delamanid, bedaquiline and/or BTZ-043 are no longer applicable with the remaining arms.

2.3.2. Benefit Assessment

While the phase 2a monotherapy study has established proof-of-principle of antituberculosis activity of GSK3036656, this will be the first study where GSK3036656 is dosed in combination with other TB drugs, including BTZ-043. The study will provide safety and tolerability data that will inform future combination studies with GSK3036656. The data from this study will also be integrated with that from other studies with the intent of ranking the drug combinations with the greatest benefit:risk profile. The most promising regimens will be taken forward into a longer study, with the aim of identifying a novel regimen for TB in addition to validating the statistical model (developed from the integrated data, and reported separately to this study). A significant proportion of people with TB fail treatment (~15% with drug-sensitive up to ~80% with XDR). New effective compounds with novel mechanisms of action are urgently needed for TB, and it is recognised as a priority area by the WHO.

A delay of treatment with the full standard regimen of 14 days is not expected to have an adverse impact on the ultimate cure of TB in these participants, and this approach has been used as part of recent successful TB drug development programs [Diacon, 2011b, Diacon, 2013]. Participants in this study will have their TB infection carefully characterized and drug sensitivity profiles established.

Participants will remain under constant medical attention and will be housed and monitored in hospital from admission through the duration of the treatment period; this will allow the continuous monitoring of the health conditions of each participant, any of whom can be withdrawn at any stage of the trial and be removed from study treatment should his/her condition suggest to the Investigator that this would be in his/her best interest. Multiple blood samples will be taken for safety laboratory studies. Upon discharge, the participants will be given the initial doses of standard TB treatment and immediately referred to the national TB treatment program local TB clinic where they will receive a full course of standard treatment. At the follow-up visit it will be confirmed that this treatment has been initiated and is being continued. The Investigators' primary responsibility is to ensure participant safety.

2.3.3. Overall Benefit: Risk Conclusion

Preliminary data support the safety profile of the selected dose of GSK3036656 in patients with newly-diagnosed TB. The known potential risks associated with GSK3036656 can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. Routine safety and tolerability will be evaluated from reported AEs, scheduled physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory test results as well as continued observation by clinical staff. The potential risks associated with the administration of GSK3036656 are considered to be justified by the potential benefits that may be afforded to patients with TB if this and future studies with GSK3036656 are deemed successful for the participants from the study treatment.

3. OBJECTIVES AND ENDPOINTS AND/OR ESTIMANDS

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 the 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).

Objectives	Endpoints
	• 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.

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

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 will be used as baseline. For all other endpoints, baseline is the last available pre-treatment assessment.

Primary EBA Estimand

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:

- 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 $CFU_{0\text{-}14}$).
- 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.

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 and will use the same strategies for the intercurrent events.

Safety Estimand

The primary question of interest is 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.

4. STUDY DESIGN

4.1. Overall Design

The study will comprise up to 8 treatment arms of participants with drug-sensitive TB. It is intended that up to 15 participants will be enrolled into each of the experimental treatment arms, currently including GSK3036656+bedaquiline, GSK3036656+delamanid, GSK3036656+BTZ-043, GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin and bedaquiline+delamanid arms, and up to 23 participants will receive standard-of-care for DS-TB (i.e. Rifafour e-275 or equivalent generic alternative).

For treatment arms GSK3036656+bedaquiline, GSK3036656+delamanid, bedaquiline+delamanid arms and standard of care, participants will be randomly assigned (3:3:3:2) to one of the four arms.

For treatment arms GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin and standard-of-care, participants will be randomly assigned (3:3:3:2) to one of four arms.

For GSK3036656+ BTZ-043 and standard-of-care, particpants will be assigned (5:1) to 1 of 2 arms. Randomisation will be stratified by eligibility for a PET-CT scan. The study will be randomized, but not blinded (i.e., it will be 'open-label') with neither participant nor Investigator blinded to treatment. Due to the different assessments being conducted for the SoC arm compared to the investigational regimens (no PET-Scans or PK sampling on the SoC arm), and the additional burden to patients if a double-dummy design were to be employed, the blinding of participants and the investigator was not considered feasible. Study participants will revert to the standard treatment for TB (i.e., Rifafour e-275 or equivalent generic alternative) once the study treatment (Day 1 to Day 14) has been completed. All laboratory staff involved in analysing and reporting the primary and secondary change in log_{10}CFU counts and TTP endpoints results will be blinded to treatment allocation.

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The spot and overnight sputum samples for measurement of RS ratio, TB-MBLA, READ-TB and PATHFAST LAM biomarkers will be part of the main study and are not considered optional.

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4.2. Scientific Rationale for Study Design

The assessment of the EBA of antituberculosis agents in sputum over the first 2 weeks of treatment is an established method for the early clinical evaluation of new antituberculosis agents and regimens [Jindani, 1980]. EBA (decline of sputum bacterial counts) is used as a potential indicator of clinical efficacy which allows the estimation of early drug effects in studies that are significantly shorter than studies using definitive clinical endpoints (e.g., relapse-free cure). However, whilst it may be indicative, early activity cannot be directly translated into longer term efficacy. CCI [redacted]

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CCI [redacted] Further information is provided in Section 6.3.

The Rifafour e-275 (or equivalent generic alternative) treatment group is included as a benchmark for the EBA quantitative mycobacteriology and to evaluate whether isoniazid/rifampicin/pyrazinamide/ethambutol (HRZE) in this population gives similar EBA results to that demonstrated in prior studies with this combination. A negative control arm, where subjects are left untreated, would be unethical due to the availability of effective treatment and the consequences of not treating TB.

4.2.1. Participant Input into Design

Participants in this study remain in hospital and do not interact with other community members as much as in longer studies with outpatients. The TASK site, where the study will be conducted, has a full-time community engagement office that runs two community advisory boards where studies such as the ones planned here are discussed, and, if deemed necessary, suitable means for informing the community are chosen.

The TASK site also maintains recruiters and treatment supporters for outpatient studies at various clinics in Cape Town. These persons are research trained and are able to provide feedback on the perception of research activities in the communities.

4.3. Justification for Dose

Bedaquiline dose justification

Based on the clinical trial and real-world data bedaquiline will be administered as per Dosing and Administration information in the Product Label (dosage in adult patients of 400 mg once daily; Sirturo Product Label, 2012). Similar to previous mono-, and combo-EBA clinical trials with bedaquiline, loading doses of 700 mg (Day 1) and 500 mg (Day 2) will be used to ensure a PK profile that more closely resembles steady-state by Day 14 [Diacon, 2013; Diacon, 2012] .

Delamanid dose justification

As indicated in the summary of product characteristics for delamanid (Deltyba. Summary of Product Characteristics, 2020), the recommended dose for treatment of MDR-TB is 100 mg twice daily. However, the future utility of a promising regimen of shorter duration will depend to a large extent on the ability to dose once daily. Given historical data from the mono-EBA trial of delamanid in which 300 mg administered once daily demonstrated the most robust activity and building from an exposure-response analysis using Phase 3 clinical trial of delamanid [Von Groote, 2019] correlating sputum culture conversion with daily exposures, the use of 300 mg once daily dose for delamanid in the evaluation of the regimen GSK3036656+delamanid is supported. From this model, the daily drug exposures corresponding to the 100 mg twice daily, 200 mg and 300 mg once daily doses were used to derive the respective distributions of probability of sputum culture conversion at each of these doses [Liu, 2018; Mallikaarjun, 2020] demonstrating that a clinical dose of 300 mg once daily closely matches the efficacy of the 100 mg twice daily dose.

QT prolongation is primarily driven by its metabolite DM-6705, which has a much longer half-life than delamanid. QTcF (QTc interval corrected for heart rate by Fridericia's formula) prolongation was approximately 50% lower for the 200 mg once daily dose than the 100 mg twice daily dose [Mallikaarjun, 2020]. The exposures of delamanid and DM-6705 following 300 mg once daily are lower than that following the 100 mg twice daily dose, indicating that the 300 mg once daily dose, much like the 200 mg once daily dose, would likely have less of an effect on a key safety issue (ie, QT prolongation) compared to the 100 mg twice daily dose.

As a result, this study will utilise a clinical dose of 300 mg once daily for delamanid.

GSK3036656 dose justification

The daily clinical dose of 20 mg of GSK3036656 was selected based on preliminary evaluation of the efficacy data from the ongoing monotherapy EBA study with GSK3036656. Exposure-Response analysis was utilised to determine the clinical steady-state exposure associated with >90% of response (change from baseline in logCFU) and this was set as the targeted clinical exposure in the present study. Furthermore, a probabilistic analysis (PTA%) using both inter-subject variability and parameters'

uncertainty was conducted to ensure that >90% of patients would achieve the targeted clinical exposure.

In addition, a translational PK/PD model and in-silico clinical trial simulations, were used to determine the exposure of GSK3036656 required to achieve PD markers within the various TB lesions (eg., MIC extracellular, MIC intracellular, MIC90, casMBC90). This allowed the comparison of the clinical targeted exposure with what is pharmacologically relevant within the site of action. [Strydom, 2019; Savic, 2017].

Based on the 2 previous analyses a daily repeat dose of 20 mg of GSK3036656 will be used in the current study with a loading dose of 50 mg on Day 1 to ensure a PK profile that more closely resembles steady-state by Day 14.

BTZ-043 dose justification

In the phase 1B/2A study, BTZ-043 was dosed on an empty stomach starting from 250 mg, to up to 1750 mg daily, for 14 days during the multiple ascending dose part (phase 1B) of that study. Doses above 1250 mg did not reach a high BTZ-043 exposure and did not have a significantly increased bactericidal activity. There were no dose-limiting AEs encountered. During the phase 2A part of that study, doses of 250, 500 and 1000 mg were given with a standard breakfast. The 1000 mg group achieved a slightly higher reduction of CFU (similar to the bactericidal activity of rifampicin) than the 2 lower doses, although not statistically significant. No dose-limiting AEs have been observed.

Preliminary dose-response and exposure-response analyses indicate that there is an inferior response in some participants at the lowest dose of 250 mg, and there is still some improvement at the higher dose, when comparing the 500 mg to the 1000 mg dose. Given the good safety profile of doses up to 1,750 mg, a dose of 1000 mg to be given approximately 30 minutes after starting to eat a standard breakfast, has been selected for this study which is the highest dose so far given to a larger number of participants.

Pretomanid dose justification

The early bactericidal activity of pretomanid has been evaluated in two 14-day studies in patients with pulmonary TB. The first EBA assessed doses of pretomanid of 200 to 1,200 mg OD [Diacon, 2012]. All doses in this range demonstrated bactericidal activity with no dose response. The second study assessed lower ranges of 50, 100, 150, and 200 mg OD [Diacon, 2012]. 50 mg of pretomanid had a lower EBA. Pretomanid was judged safe and well tolerated, although the incidence of adverse events (AEs) potentially related to pretomanid appeared dose related. Thus, the range of 100 to 200 mg was identified for further evaluation of pretomanid in novel antituberculosis regimens [Nedelman JR, 2020]. Pretomanid 200 mg has been adopted as the dose in the WHO approved BPaLM regimen.The study will use the labelled dosing of 200 mg pretomanid OD.

Moxifloxacin dose justification

Moxifloxacin caneither be dosed by weight (between 400-800 mg) or at a fixed dose 400 mg, as indicated in the summary of product characteristics for moxifloxacin [Moxifloxacin. Summary of Product Characteristics Mofloxacin, 2023]. With weight-based dosing potential of maximising efficacy has to be weighed up against potential for increased cardiac toxicity. In the STREAM stage 1 trial 282 participants taking short course therapy containing moxifloxacin (dosed between 400-800 mg dosed by weight) along with clofazimine (which also prolongs the QT interval) were compared to 142 participants taking WHO long course therapy where moxifloxacin (dosed at 400 mg in all weight bands) or levofloxacin was used without other drugs with a major effect on QT interval. Those with QTc ≥ 500 ms at baseline were ineligible for the trial. During the trial those in the short course experienced a median maximum change of 50 ms (IQR 36-65) vs 30ms (IQR 22-41) in the long course, with 11% in the short course arm vs 6.4% in the long course arm progressing to QT or QTc ≥ 500 ms, although the difference was not significant(p=0.14) [Hughes G, 2022]. In this study a fixed dose of 400 mg per day will be used, to minimise cardiac toxicity. This is similar to the dosing of moxifloxacin as part of the WHO approved BPaLM regimen. [World Health Organisation, 2022].

Linezolid dose justification

The ZeNix trial evaluated four different dose/duration combinations of Linezolid in the BPaL regimen; 1200 mg for either 2 or 6 months or 600 mg for 2 or 6 months. Peripheral neuropathy was reported in 38% in the of arm taking 1200 mg for 6 months vs 13% in the 600 mg for 2 months arm. Myelosuppression, manifest by anaemia was observed in 22% in the 1200 mg for 6-month arm vs 7% in the 600 mg for 2 months arm. Overall efficacy was comparable at 93% in the arm taking 1200 mg for 6 months and 84% in the arm taking 600 mg for 2 months. Following the results of the TB-PRACTECAL study, the BPaLM regimen has been recommended for the treatment of RR/MDR-TB by the WHO in 2022, this includes linezolid dosed at 600 mg OD. [Nyang'wa BT, 2022]. Furthermore an EBA study comparing linezolid 600 mg OD versus linezolid 600 mg BD did not show differences in EBA at 0-2 and 2-7 days [Dietze R, 2008]. In this study we will therefore use Linezolid at a dose of 600 mg OD to minimise adverse events [World Health Organisation, 2022]

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit (the ‘follow-up’ visit). A participant is considered to have completed the study treatment phase once they have received the final dose of study treatment on Day 14.

The end of the study is defined as the date of the last visit of the last participant in the study.

Following completion of the study treatment phase and after discharge from hospital the participants will be provided with their first dose/s of standard TB therapy with appropriate counselling. All participants will be referred to the local community TB

clinics to receive the remainder of a full course of standard antituberculosis chemotherapy according to national guidelines. The participants will be provided with a referral letter to take with them to the TB clinic.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be 18 to 65 years of age inclusive, at the time of signing the informed consent. However, only participants who are at least 25 years of age (and females of non-childbearing potential) will be eligible for the PET-CT assessments.

Type of Participant and Disease Characteristics

2. Participants who have:

   New episode of untreated, rifampicin-susceptible pulmonary TB

   A chest x-ray picture which in the opinion of the Investigator is consistent with TB

   At least 1 sputum sample positive on direct microscopy for acid-fast bacilli (at least 1+ on the International Union Against Tuberculosis and Lung Disease [IUATLD]/WHO scale) or positive on a molecular test (at least medium positive for MTB on Xpert MTB/Rif Ultra)

   Ability to produce an adequate volume of sputum as estimated from an overnight sputum collection sample (estimated 10 mL or more). If less than 10 ml is collected overnight this may be repeated once.

   Normal echocardiogram or echocardiogram with normal left ventricular function with at most trace to mild valvular regurgitation is allowed and no valvular stenosis.

   A creatinine clearance ≥75 mL/min (Cockroft-Gault formula).

Weight

3. Body weight (in light clothing and with no shoes) within 40-90kg inclusive.

Sex and Contraceptive/Barrier Requirements

4. Male and females of childbearing potential

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 90 days, after the last dose of study intervention:

- Refrain from donating fresh unwashed semen

  Plus

  - Must agree to use contraception/barrier as detailed below
    - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
    - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

b Female Participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4 Contraception and Barrier Guidance

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 during the study intervention period and for at least 14 days after the last dose of study intervention [and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period]. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test urine or serum as required by local regulations within 24 hours before the first dose of study intervention (see Section 8.3.5: Pregnancy Testing).
  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5. Pregnancy Testing
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Evidence of a clinically significant (as judged by the Investigator) condition or abnormality (other than the indication being studied) that might compromise safety or the interpretation of trial efficacy or safety endpoints.
2. Poor general condition where any delay in treatment cannot be tolerated per discretion of the Investigator.
3. Clinically significant evidence of extrathoracic TB as judged by the Investigator.
4. QTcF > 450 msec.
5. History of allergy to any of the trial IP/s or related substances as confirmed by the clinical judgement of the Investigator.
6. Participants with vitiligo.
7. Current alcohol or drug abuse, that is, in the opinion of the Investigator, sufficient to compromise the safety or cooperation of the participant.
8. Participants receiving any QT prolonging drugs, including but not limited to fluoroquinolones, macrolides and clofazimine.
9. HIV infected participants:
    a. having a CD4+ count <350 cells/µL;
    b. or having received efavirenz or lopinavir-boosted ritonavir as antiretroviral therapy medication within the last 30 days;
    c. or having received oral or intravenous antifungal medication within the last 30 days;
    d. or with an AIDS-defining opportunistic infection or malignancies [CDC, 1993] in the last 12 months (except pulmonary TB).
10. Presence of Hepatitis B surface antigen (HBsAg) or Positive Hepatitis C antibody test result at screening.
11. Participants with Type 1 diabetes. Participants with non-type 1 diabetes with sub optimal glycemic control (HbA1c above 7 %), receiving insulin or more than one glucose lowering agents. Diabetic participants that have not performed diabetic eye screening within the last 12 months should be excluded.

12. Any diseases or conditions in which use of delamanid or bedaquiline is contraindicated, to include
    - Cardiovascular disease such as myocardial infarction, heart failure, coronary heart disease, clinically significant arrhythmia, tachyarrhythmia, or pulmonary hypertension
    - Long QT syndrome or family history of long QT syndrome or sudden death of unknown or cardiac-related cause
13. Participants with the following abnormal laboratory values at screening as graded by the enhanced Common Terminology Criteria for Adverse Events (CTCAE v 5 2017):
    a. haemoglobin <8.0 g/dL;
    b. thrombocytopenia grade 2 or greater (under 50×10^9 cells/L);
    c. alanine aminotransferase (ALT) grade 2 (≥2.0 × ULN);
    d. serum total bilirubin >1.5xULN
    e. total white cell count grade 3 (<2.0×10^9 cells/L)
    f. hypoalbuminaemia (<1.8g/dL)
15. Any diseases or conditions in which there are special warnings or contrindications relating to the use of moxifloxacin, to include:
    a. Prior tendon disorder related to fluoroquinolone use.
    b. History of epilepsy.
    c. Myasthenia gravis.
    d. Peripheral neuropathy.
    e. Family history of aneurysm disease;
    f. Pre-existing aortic aneurysm and/or aortic dissection or risk factors or conditions predisposing to aortic aneurysm and dissection (e.g., Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, and known atherosclerosis).
    g. Prior *Clostridioides difficile* colitis.
16. History of ocular abnormalities, including cataracts or retinopathies of any origins.

Prior/Concomitant Therapy

17. Treatment received with any drug active against Mtb (excluding amoxicillin but including but not limited to isoniazid, ethambutol, fluoroquinolones, rifampicin), or with immunosuppressive medications such as TNF-alpha inhibitors or systemic corticosteroids (used for > 5 consecutive days), within 2 weeks prior to screening. Refer to the SRM for details.
18. Unavoidable treatment with prohibited concomitant medications (see SRM)

Prior/Concurrent Clinical Study Experience

19. Participated in other clinical studies with investigational agents within 8 weeks prior to the first dosing day in the current study.
20. Participants who have previously received any of the following: GSK3036656 or pretomanid.
21. Participants who may have received moxifloxacin or linezolid within 90 days from screening.

Diagnostic Assessments

22. Participants aged 25 years or above who undergo FDG-PET/CT who have been estimated to have been exposed to ionising radiation in excess of 10 mSv above background over the previous three-year period as a result of occupational exposure to radiation or as a result of research studies. This will be judged through clinical history taking.

Other Exclusions

23. Lactose intolerance or lactase deficiency
24. Participants unable or unwilling to adhere to study requirements.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, from the day of start of study treatment until after the final dose.
- Water is allowed ad libitum.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will refrain from consuming caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

There is no reason for enrolment to be delayed in this study when inclusion/exclusion criteria are met.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

An overview of the study interventions and study arms are provided in Table 2 and Table 3.

Table 2 Study Intervention(s) Administered

Study Intervention Name:	GSK3036656	Delamanid	Bedaquiline	BTZ-043	Moxifloxacin	Pretomanid	Linezolid	Rifafour e-275 (or equivalent generic alternative)
Dosage formulation:	Capsule	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	5/25 mg/20 mg (as free base equivalent) Loading dose 50 mg on Day 1	50/300 mg	100/400 mg Loading dose 700 mg on Day 1 and 500 mg on Day 2	250 mg/1000 mg	200 mg/400 mg	200 mg/200 mg	200 mg/600 mg	Standard dose: 150/75/400/275 mg of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol respectively per tablet
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Dosing instructions:	Refer to study reference manual	Refer to study reference manual	Refer to study reference manual	Refer to study reference manual	Refer to study reference manual	Refer to study reference manual	Refer to study reference manual	Refer to South African National TB

Study Intervention Name:	GSK3036656	Delamanid	Bedaquiline	BTZ-043	Moxifloxacin	Pretomanid	Linezolid	Rifafour e-275 (or equivalent generic alternative)
								Treatment Guidelines (including pyridoxine as required)
Manufacturer	WuXi AppTec contracted by GSK (5/25 mg capsules)	Otsuka	Janssen-Cilag	GenPlus contracted by Klinikum of LMU	Bayer AG	TB Alliance	Sandoz Ltd	Rifafour e-275: Sanofi-Aventis or appropriate alternative Equivalent Generic alternative to Rifafour e-275: Appropriate suppliers
IMP and NIMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	NIMP
Sourcing	Provided centrally by the sponsor	Commercial material sourced	Commercial material sourced	Provided centrally by the sponsor	Commercial material sourced	Commercial material sourced	Commercial material sourced	Commercial material sourced

Study Intervention Name:	GSK3036656	Delamanid	Bedaquiline	BTZ-043	Moxifloxacin	Pretomanid	Linezolid	Rifafour e-275 (or equivalent generic alternative)
		locally by the study site	locally by the study site		locally by the study site	locally by the study site	locally by the study site	locally by the study site
Packaging and Labelling	Study Treatment will be provided in HDPE bottles. Each HDPE bottle will be labelled as required per country requirement.	Study treatment will be labelled as required per country requirement	Study treatment will be labelled as required per country requirement	Study Treatment will be provided in HDPE bottles. Each HDPE bottle will be labelled as required per country requirement.	Study treatment will be labelled as required per country requirement	Study treatment will be labelled as required per country requirement	Study treatment will be labelled as required per country requirement	Will be provided by the manufacturer.
Current/Former Name(s) or Alias(es)]		Deltyba	Sirturo		Avelon Moxibay	Dovprela	Zyvoxid Elturin	

Table 3 Study Arm(s)

Arm Title	GSK3036656 + delamanid	GSK3036656 + bedaquiline	GSK3036656 + BTZ-043	Delamanid + bedaquiline	GSK3036656 + Moxifloxacin	GSK3036656 + Pretomanid	GSK3036656 + Linezolid	Standard of care for DS-TB
Arm Type	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental	Control
Arm Description	Participants will receive GSK3036656 20 mg once daily + delamanid 300 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1	Participants will receive GSK3036656 20 mg + bedaquiline 400mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1. A loading dose of 700 mg bedaquiline will be given on Day 1 and 500 mg on Day 2. Participants will receive 400 mg bedaquiline on Days 3 to 14	Participants will receive GSK3036656 20 mg + BTZ-043 1000 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1.	Participants will receive Delamanid 300 mg once daily + bedaquiline 400 mg once daily for 14 days. A loading dose of 700 mg bedaquiline will be given on Day 1 and 500 mg on Day 2. Participants will receive 400 mg bedaquiline on Days 3 to 14	Participants will receive GSK3036656 20 mg + moxifloxacin 400 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1.	Participants will receive GSK3036656 20 mg + pretomanid 200 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1.	Participants will receive GSK3036656 20 mg + linezolid 600 mg once daily for 14 days. A loading dose of 50 mg GSK3036656 will be given on Day 1.	Participants will receive Rifafour e-275 (or equivalent generic alternative) once daily for 14 days

6.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study intervention. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study without masking for all treatment arms however, to reduce potential bias, the study will be randomised and the randomisation will be stratified based on eligibility for PET/CT scans. Of note, no subjects randomised to the SoC arm, regardless of eligibility (randomisation strata), will undergo a PET-CT scan.

The initial 4 treatment arms i.e., GSK3036656+bedaquiline, GSK3036656+delamanid, bedaquiline+delamanid and Standard of care (SoC) have already been randomized with the ratio of 3:3:3:2.

GSK3036656+BTZ-043 and SoC will be randomized to a ratio of 5:1. The GSK3036656+BTZ-043 arm may start prior to the approval of protocol amendment 3, and thus initial recruitment will be to the GSK3036656+BTZ-043 arm only. Once the amendment is approved, or when 9 participants have been recruited (whichever occurs first), the remaining participants yet to be enrolled will be randomised (pausing recruitment until approval of the amendment if necessary) to GSK3036656+BTZ-043 or SoC, ensuring the overall ratio is 5:1. For eg., if 6 partcipants have already received GSK3036656+BTZ-043, the remaining participants will be randomised 3:1 (9 to GSK3036656+BTZ-043 and 3 to SoC).

The other 4 treatment arms GSK3036656+pretomanid, GSK3036656+linezolid, GSK3036656+moxifloxacin and Standard of Care (SoC) will be randomized to ratio 3:3:3:2.

The randomisation schedule will be generated by GSK using Randall NG. The site pharmacist will receive a copy of the randomisation schedules from the GSK Randomisation team co-ordinator to enable dispensing of study medication.

Prior to Day 1, once eligibility has been confirmed, participants will be assigned a unique randomisation number in ascending numerical order, according to the randomization schedule generated prior to the study by the Statistics Department at GSK, using validated internal software. The PI or delegated responsible person will assign the randomisation numbers and the randomisation number will be entered in the case report form (CRF). Once assigned, a randomization number must not be reassigned to another participant in the study. For participants who are replacements, a replacement randomization number will be provided as detailed in the SRM.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site staff will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Dose modification is not permitted.

6.6. Continued Access to Study Intervention after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study.

6.7. Treatment of Overdose

For this study, the following will be considered an overdose;

- Any dose of GSK3036656 greater than 20 mg within a 24-hour time period,other than the loading dose of 50 mg on Day 1,will be considered an overdose.

- Any dose of BTZ-043 greater than 1000 mg within a time period until before the scheduled next dose, will be considered an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 14 days).
3. CCI [redacted]
   CCI [redacted]
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

The sponsor does not recommend specific treatment for an overdose.

In addition;

- For this study, any dose of bedaquiline greater than 400 mg within a 24-hour time period, other than the loading dose of 700 mg on Day 1 and 500 mg on Day2, will be considered an overdose. In case of overdose, participants should be carefully observed including vital signs and ECG monitoring. It is recommended that the appropriate supportive care should be administered.

- For this study, any dose of delamanid greater than 300 mg within a 24-hour time period will be considered an overdose. Treatment of overdose should involve immediate measures to remove delamanid from the gastrointestinal tract and supportive care as required. Frequent ECG monitoring should be performed.

- For this study, any dose of pretomanid greater than 200 mg within a 24-hour time period will be considered an overdose. In case of overdose, participants should be carefully observed including vital signs and ECG monitoring. It is recommended that the appropriate supportive care should be administered.

- For this study, any dose of moxifloxacin greater than 800 mg within a 24-hour time period will be considered an overdose. In case of overdose, charcoal should be given within 6 hours from ingestion, participants should be carefully observed including vital signs and ECG monitoring. It is recommended that the appropriate supportive care should be administered.

- For this study, any dose of linezolid greater than 1200 mg within a 24- hour time period will be considered an overdose in case of overdose, charcoal should be

given within 6 hours from ingestion, participants should be carefully observed including vital signs. It is recommended that the appropriate supportive care should be administered.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study. A list of prohibited and permitted concomitant medication is provided in the SRM.

Paracetamol/Acetaminophen, at doses of ≤4 grams/day, is permitted for use any time during the study except for participants receiving BTZ-043. Participants receiving BTZ-043 are permitted to use ≤2 grams/day. Ibuprofen at doses of 400 mg up to 3 times per day is also permitted if needed. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will be withdrawn from the study and will be asked to complete an Early Discontinuation Visit. Early discontinuation discharge procedures are listed in Section 7.2 See the SOA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Stopping Criteria

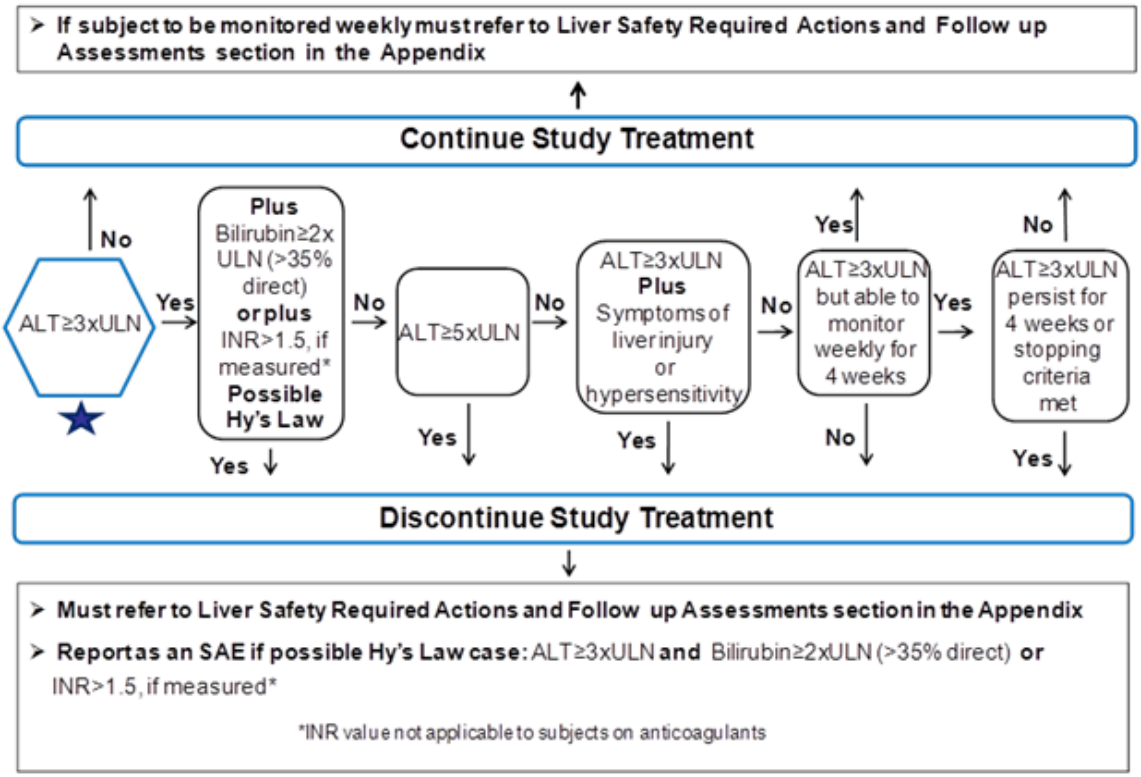
Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets the condition outlined in the algorithm below or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Phase 2 Liver Chemistry Stopping and Increased Monitoring Algorithm



Refer to Section 10.5. for required Liver Safety Actions and Follow up Assessments.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrolment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Withdrawal of participants is to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period of time (less than 10 minutes) and then use the averaged QTcF values of the three ECGs to determine whether the subject should be discontinued from the study.

A participant that meets either bulleted criterion below based on average QTc values of triplicate ECGs over a brief recording period will discontinue study intervention and will be withdrawn from the study.

- QTcF >500 msec,
- Change from baseline in healthy participants: QTcF >60 msec

See Section 8.3.3 for additional details of obtaining ECGs.

7.1.3. Haematology Stopping Criteria

IP will be discontinued for a subject if the following haematology stopping criteria are met (confirmed on 2 samples or at the discretion of the investigator in consultation with the medical monitor) and participants should be followed up until values are not clinically significant.

- A reduction in haemoglobin to below 6.0 g/dL
- A reduction in neutrophil count to below 500/mm^3 (0.5 × 109/L)

Patients with a confirmed haemoglobin <8.0g/dL after randomisation will require enhanced observations, with a repeat haemoglobin level and discussion of patient status with the GSK medical monitor.

7.1.4. Temporary Discontinuation

Temporary discontinuation of study intervention in this study is not permitted. If the participant has to stop study intervention for any reason, then this will be considered as an early withdrawal from study treatment.

7.1.5. Rechallenge

Study intervention restart or rechallenge after any of the stopping criteria are met (i.e., study treatment discontinued) by any participant in this study is not allowed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SoA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative procedures

8.1.1. Collection of demographic data

Record demographic data such as year of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.2. Microbiological Efficacy/Activity Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

The EBA CFU0-14 as determined by the change from baseline to day 14 in log10CFU per mL sputum will be summarised and described with a statistical model for participants in each group. The change from baseline at each available timepoint will also be summarised and displayed graphically.

The EBA TTP0-14 as determined by the change from baseline to day 14 in TTP per mL sputum will be summarised and described with a statistical model for participants in each group. The change from baseline at each available timepoint will also be summarised and displayed graphically.

For the purposes of the microbiological endpoints assessments, the pre-treatment baseline will be defined as the mean of Day -2 and Day -1; if data is available at only one of these timepoints then that value will be used as baseline, and data prior to Day −2 will not be used to calculate the mean at baseline.

Mycobacterial Characterisation:

The identifying organism will be confirmed as Mtb at least once by polymerase chain reaction (PCR) at screening (GeneXpert or Line Probe) and a sample collected before treatment will be submitted for culture confirmation.

Drug susceptibility testing of Mtb for sensitivity to rifampicin with a molecular method will be tested at the screening visit (GeneXpert) to determine eligibility. Susceptibility to rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB) will be confirmed on a culture grown from a sample collected before treatment either by phenotypical testing or line probe.

Cultures from baseline and from day 14 sputum will be kept for determination of the minimum inhibitory concentration (MIC) of the investigational agents that the subject was treated with. If a day 14 culture is not available, the last available culture after day 8 will be kept. In the event of significant changes in the MIC, bacterial isolates will be sent to the GSK Spain laboratory for further characterisation, or in the case of a change in MIC for BTZ-043, to a laboratory designated by the developer of that drug. Technical details are provided in the SRM. MIC data reporting will likely occur after the clinical database has been authorised for the primary and secondary efficacy and safety endpoints at the end of the study (i.e., after Database Freeze [DBF]). The report detailing the data will remain as a separate report and will not be included in the GSK clinical study report.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- An assessment of the skin will be undertaken as part of the physical examinations. Further information is provided in the SRM.
- Investigators must pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Position of the participant should be consistent across readings (e.g., semi-supine or supine). Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements must be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

- Vital signs (to be taken before blood collection for laboratory tests) will consist of at least 1 pulse and 1 blood pressure measurement. Where a measurement is abnormal or significantly different from previous measurements, a further 2 readings will be taken. When vital signs are measured in triplicate, values should be taken at least 1 minute but not more than 5 minutes apart and recorded in the CRF.

8.3.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, uncorrected QT intervals. QTcF will be calculated using heart rate and QT by Friderica's formula (see SRM). Also refer to ECG stopping criteria listed in Section 7.1.2.
- At Screening, ECGs will be measured in triplicate. In the event where triplicate ECG readings are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 10 minutes and the QTc must be based on the average of triplicated ECG readings.

  Stopping criteria are in Section 7.1.2.

At all other timepoints, a single ECG measurement should be taken.

8.3.4. Clinical Safety Laboratory Tests

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 24 hours after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3)

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted as described in the SoA during study intervention period. The pregnancy test at Screening must be serum as described in the SoA.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 14 days and correspond with the time frame for female participant contraception in Section 5.1 Inclusion Criteria
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant’s participation in the study.

8.3.6. Visual Assessments

- Visual acuity and colour vision (e.g. Ishihara plate) examination will be performed as outlined in the SoA at screening.
- The following visual assessments will be carried out prior to randomisation

    - Visual acuity and colour vision will be assessed by standard methods.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) or serious adverse events (SAEs) can be found in Section 10.3.1 and Section 10.3.2.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention until the follow-up visit at the timepoints specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up visit at the timepoints specified in the SoA (Section 1.3).

  Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the medical history/current medical conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

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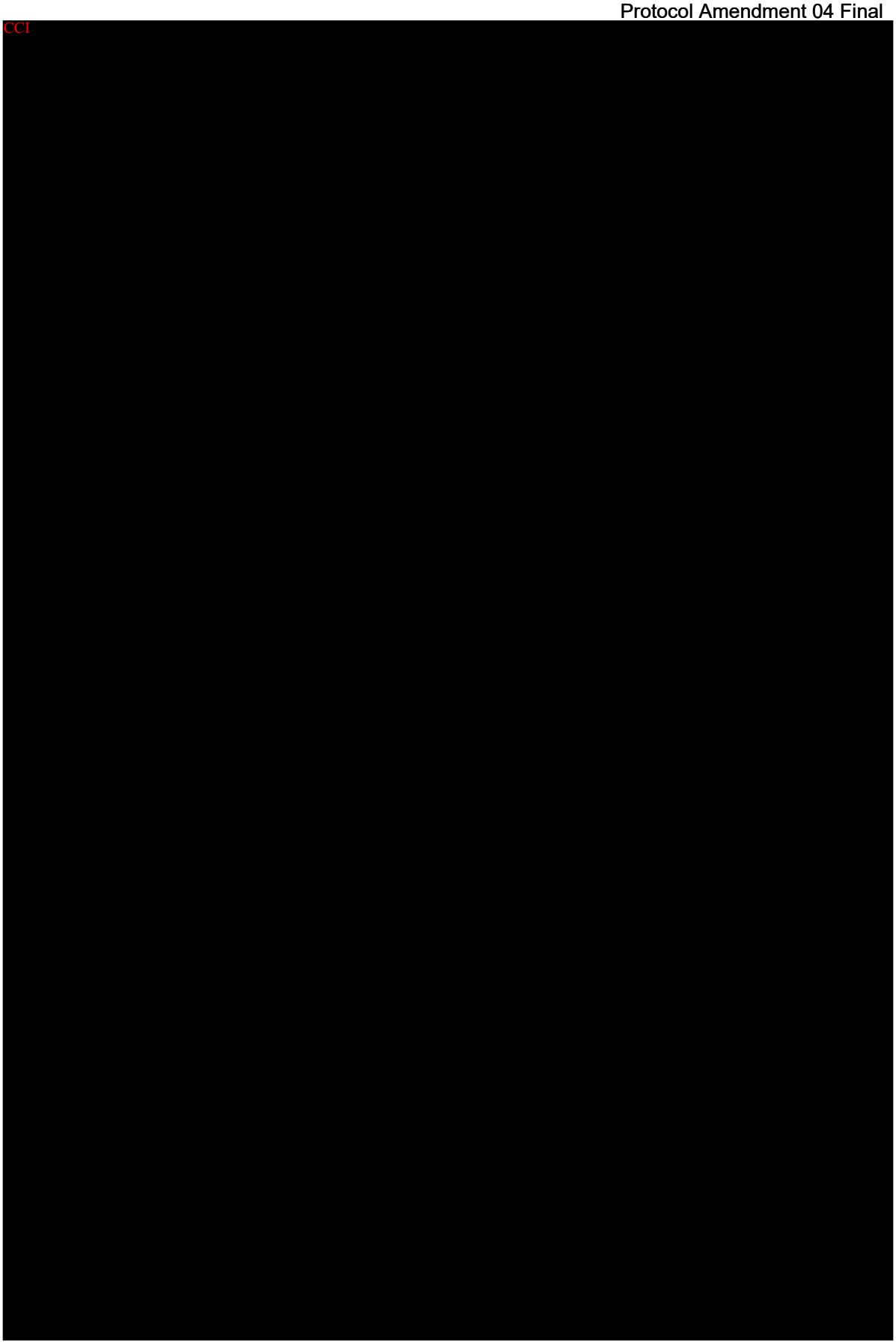
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8.6. Genetics

Genetics are not evaluated in this study.

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9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to database release and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

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, linezolid or moxifloxacin. No between treatment group statistical comparisons are planned, though the results will be compared qualitatively. No hypotheses are therefore defined. Within each treatment group a decrease in $\log_{10}$CFU 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.

The data collected within this study will be provided to TASK for use in their statistical modelling, integrating the data with that from other similar EBA studies. This modelling is being performed to rank different regimens and to assess the ability of EBA studies to

predict the longer-term efficacy of TB treatment combinations, and hence to establish effective development pathways for future TB treatments.

9.1.1. Multiplicity Adjustment

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

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Screened	All participants who were screened for eligibility.
Enrolled	All participants who passed screening and entered the study.
Safety	All participants who received at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.
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 were randomised to.
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9.3. Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.3.1. General Considerations

The efficacy analysis set will be used for the summaries and analyses of EBA and PKPD endpoints; the safety analysis set will be used for the summaries and analyses of safety endpoints and assessments; the PK analysis set will be used for the summaries and analyses of PK concentrations and parameters.

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.

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.

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 will be used as baseline. For all other endpoints, baseline will be the last available pre-treatment assessment unless otherwise specified in the statistical analysis plan.

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.

9.3.2. Primary Endpoint Analysis

The primary endpoint is the change from baseline to Day 14 in log10CFU. This will be estimated separately for each of the 5 treatment groups; between treatment group differences will not be estimated. Of note, the SoC arm is included to qualitatively assess the internal assay sensitivity of the study, not for comparison with the 4 investigational treatment groups. The estimand for the primary endpoint analysis is defined in Section 3.

Change from baseline in $\log_{10}$CFU per ml direct respiratory sputum will be summarised and plotted, by timepoint, for each treatment group, for the efficacy population. Changes from baseline to Day 14 will be analysed using a mixed model with repeated measures (MMRM), including treatment, baseline, day, BMI, baseline-by-day and treatment-by-day as covariates. Estimates of the change from baseline to Day 14, together with 95% confidence intervals, for each treatment group will be obtained from the model. The results will be compared qualitatively, but no formal between treatment groups comparisons will be performed.

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.

Additional sensitivity analyses may be described in the SAP.

9.3.3. Secondary Endpoint Analysis (EBA Endpoint)

The analysis of the change from baseline to Day 14 in time to sputum culture positivity (TTP) will be analogous to that described in Section 9.3.2.

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9.3.5. Safety Analysis

The attributes of the estimand for the analysis of the safety endpoints are defined in Section 3.

Safety data will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. The safety population will be used for all safety analyses.

The values of potential clinical importance (PCI) for laboratory parameters, ECGs and vital signs will be detailed in the SAP.

9.3.5.1. Adverse Events (AEs)

Adverse event reporting will be performed using the MedDRA (Medical Dictionaries for Regulatory Activities) coding system. 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

9.3.5.2. Electrocardiograms (ECGs)

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.

9.3.5.3. Clinical Laboratory Values

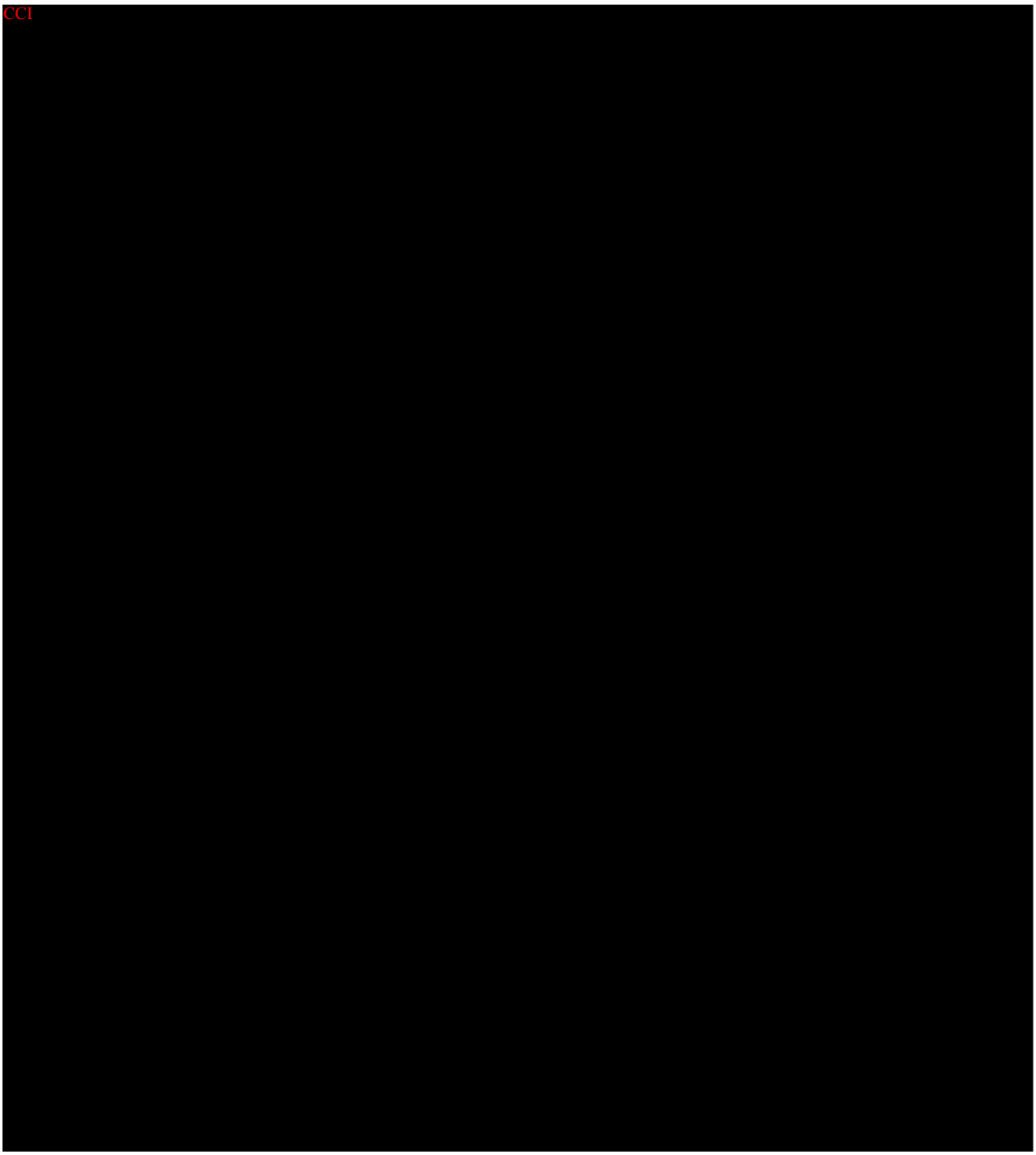
Haematology and clinical chemistry laboratory data, relative to PCI criteria, will be summarized by treatment group, laboratory test and category. The summary will present the worst case post-baseline data, relative to baseline data, by PCI category, for each participant.

9.3.5.4. Vital Signs

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.

9.3.6. Other Analysis

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9.4. Interim Analysis

Two interim analyses have been planned for this study.

The first Interim will be conducted after completion of all subjects in GSK3036656 + delamanid and GSK3036656 + bedaquiline arms prior to the completion of the other arms within the study. 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.

The second Interim will be conducted after completion of all subjects in GSK3036656 + BTZ-043 arm to inform inclusion of a four drug regimen containing BTZ-043 and GSK3036656 in the Phase 2B/C UNITE4TB PARADIGM4TB study.

For each interim analysis, data from all completed treatment arms (including the concurrent SoC arm) will be analysed. Data from ongoing treatment arms will be excluded from the interim analyses.

9.5. Sample Size Determination

Up to 15 participants will be 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 will be enrolled into the SoC arm. For purposes of randomization, the SoC treatment arm will be split into 3 parts, as indicated in Section 6.3. Up to 10 participants will be enrolled into the first and third parts of the standard of care arm, until at least 8 have completed the 14 day assessments. 3 participants will be enrolled into the second standard of care arm.

No formal treatment comparisons are planned for this study, all analyses will be descriptive in nature. However, the following table describes the precision of a 2 sided 95% confidence interval (CI), for the mean change in $\log10CFU_{(0\text{-}14)}$, 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 log10CFU(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.

9.5.1. Sample Size Sensitivity

If the standard deviation is greater than anticipated, the 95% CIs for the mean change from baseline to Day 14 in log10CFU 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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:

  Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines

  Applicable ICH Good Clinical Practice (GCP) guidelines

  Applicable laws and regulations

- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

- The investigator will be responsible for the following:

  Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC

  Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures

  Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable),), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risk and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protect requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.
- If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.

A participant who is rescreened is not required to sign another ICF.

GSK (alone or working with others) may use participant’s coded study data and samples and other information to carry out this study; understand the results of this study; learn more about the study intervention or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the the study intervention approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding “No” box and will not provide this separate signature.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Internal Safety Review Committee

- Participant safety will be continuously monitored by the sponsor's internal safety review committee, which includes safety signal detection at any time during the study
- All safety data collected will be summarized and reviewed by the sponsor's internal safety review for agreement of next steps.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients' received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in eCRF Completion Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Report to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or

institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

- When copies of source documents are shared externally for review by a central reader mechanism (e.g., expert reader), documents are stored by the external body for a minimum of 7 years**.**

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g. expert reader). The non-exhaustive list of documents shared to inform the central reader may include, imaging reports, treatment assignment etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first centre initiated and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally

support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 4 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Protocol-required Safety Laboratory Tests

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet count
RBC count
Hemoglobin
Hematocrit
Coagulation test (INR, PT, APTT)</td><td colspan="2">RBC Indices:
MCV
MCH
%Reticulocytes</td><td>WBC count with differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="3">Clinical Chemistry[1]</td><td>BUN</td><td>Potassium</td><td>Aspartate aminotransferase (AST)</td><td>Total, indirect and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td rowspan="2">Alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactic dehydrogenase (LDH), sodium, potassium, calcium (corrected for albumin), chloride</td><td>Total protein

Albumin</td></tr>
<tr><td>Glucose (random/fasting)</td><td>Calcium (corrected for albumin)</td><td>Alkaline phosphatase[2]</td><td>Magnesium</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• Specific gravity
• pH, glucose, protein, blood, micro-albumin, ketones, bilirubin, urobilinogen, nitrite, sodium, leukocytes by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Pregnancy testing</td><td colspan="4">• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]</td></tr>
</table>

Laboratory Assessments	Parameters
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Urine drug screen (to include at minimum: amphetamines, cocaine, opiates) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.5 All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements,visual assessments), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism

Cardiovascular Events (CV) Definition:

- Deep venous thrombosis/pulmonary embolism
- Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

Assessment of Causality

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Injectable hormonal contraceptive

Highly Effective Methods[b] That Are User Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. Male condoms must be used in addition to hormonal contraception If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Elevated liver enzymes, transient liver dysfunction, hepatotoxicity and hepatitis are listed as side-effects in the package inserts for Rifafour e-275 [Rifafour, 2002] or equivalent generic alternative, associated with multiple drug components. Therefore, participants allocated to Rifafour e-275 (or equivalent generic alternative) treatment who experience Liver Chemistry Stopping criteria are not mandated in the first instance to undergo those follow-up assessments (which are intended to investigate aetiology). The investigations may still be performed, if required in the judgement of the investigator.

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver chemistry event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted (see below)</td><td><u>For all study participants:</u>
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Record alcohol use on the liver event alcohol intake case report form (CRF) page *<u>For all participants except SOC arm</u>* • Viral hepatitis serology[4] • Obtain blood sample for pharmacokinetic (PK) analysis as soon as possible, and certainly within 14 days after last dose [5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia **<u>For bilirubin or INR criteria:</u>** *<u>For participants on GSK3036656 arm only</u>* • Auto-immune screen: Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum paracetamol/acetaminophen adduct high performance liquid chromatography (HPLC) assay or enzymatic/colorimetric assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James,2009]). • Liver imaging (ultrasound, magnetic resonance, or

Liver Chemistry Stopping Criteria	
	computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

For PK sampling; record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Liver chemistry criteria for a Liver Monitoring Event and follow-up actions:

These Increased Monitoring Criteria apply to all participants who experience a Liver Event, regardless of which treatment the participant has been randomized to.

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3×ULN and <5×ULN **and** bilirubin <2×ULN, **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality by email or phone to discuss participant safety. • Participant can continue study intervention. • Participant must return weekly for repeat liver chemistries (ALT, AST, ALP, bilirubin) until they resolve, stabilise or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
	• If, after 4 weeks of monitoring, ALT <3×ULN and bilirubin <2×ULN, monitor participant twice monthly until liver chemistries normalize or return to within baseline

The site will complete the liver event eCRF (Monitoring Event) in InForm and should also consider whether the AE reporting guidelines apply.

10.6. Appendix 6: Radiation Dose

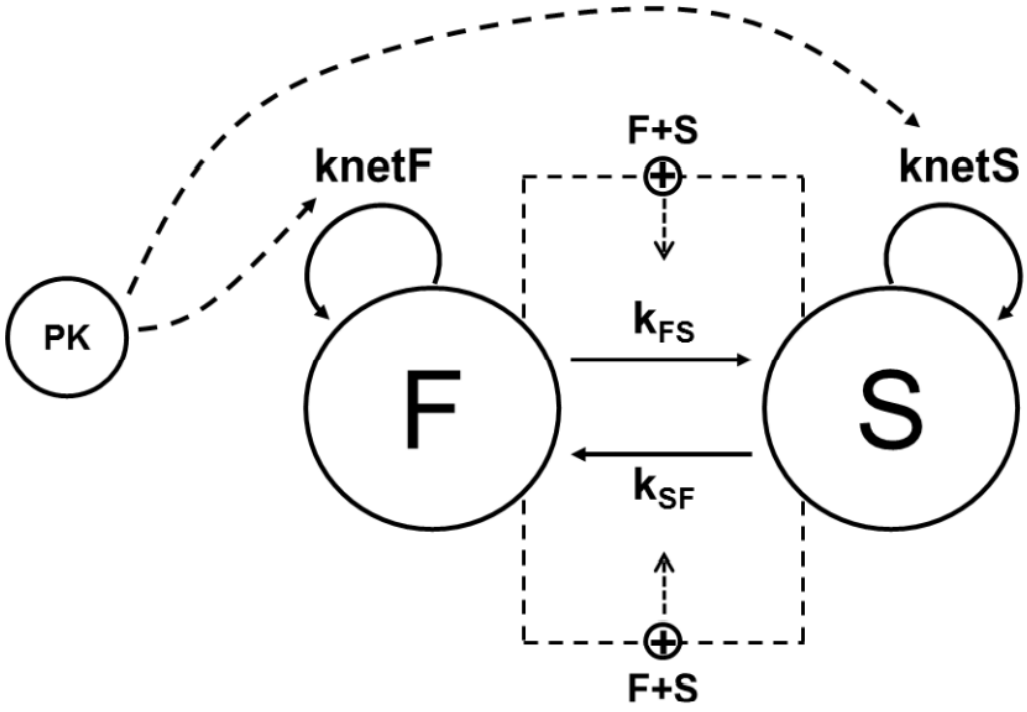
Subjects may be exposed to an additional dose of ionising radiation as a consequence of their participation in this study. The ionising radiation exposure from PET/CT scanning comes from 3 sources. A proportion of the radiation exposure comes from the administered radioligand ([18F]-FDG). The remaining radiation dose comes from high resolution CTs (HRCT) for anatomical localisation and lesion segmentation and low dose CT scans performed in order to correct the PET data for tissue attenuation (AC-CT). The doses chosen for this study aim to deliver a minimal radiation exposure, compatible with a good quality PET and CT signal.

Each subject will have up to 2 scans, each comprising 1 [18F]-FDG administration, once HRCT and 1 AC-CT. The effective dose for each radioligand administration will be 4.67 mSv based on a maximum administered activity of 260 MBq (7 mCi). A low-dose AC-CT scan of the lung results in an effective dose of 0.79 mSv and an HRCT scan results in an effective dose of 5.4 mSv. The total effective dose to each participant will therefore be up to 2 x (4.67 + 0.79 + 5.4) = 21.7 mSv. All of this exposure is over and above standard practice.

CCI

[redacted]

A schematic of the model is shown below;



10.8. Appendix 8: Abbreviations and Trademarks

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALARP	As low as reasonably practicable
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration Time Curve
AUC0-24	Area Under the Plasma Concentration Time Curve from Zero to End of Dosing Interval
BPaL	Bedaquiline Pretomanid Linezolid
Bpm	Beats per min
CA	Competent Authority
CFU	Colony Forming Units
CONSORT	Consolidated Standards of Reporting Trials
CPMS	Clinical Pharmacology Modeling and Simulation Department
Cmax	Maximum Observed Plasma Concentration
CRF	Case Report Form
CSR	Clinical Study Report
CCI [redacted]	
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DRF	Dose Range Finding
DS	Drug Sensitive
DZIF	German Centre for Infection Research
EBA	Early Bactericidal Activity
EC	Ethics Committee
ECG	Electrocardiogram
ED	Early Discontinuation
EMB	Ethambutol
EWV	Early Withdrawal Visit
CCI [redacted]	
FTIH	First Time-In Human
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HR	Heart Rate
HRCT	High Resolution Computed Tomography
HRZE	Isoniazid/Rifampicin/Pyrazinamide/Ethambutol
IB	Investigator's Brochure

ICF	Informed Consent Form
IDSL	Integrated Data Standards Library
IV	Intravenous
IP	Investigational Product
IUATLD	International Union Against Tuberculosis and Lung Disease
INH	Isoniazid
INR	International Normalised Ratio
LAM	Lipoarabinomannan
LDH	Lactate Dehydrogenase
MBLA	Molecular Bacterial Load Assay
MDR	Multi Drug Resistant
MedDRA	Medical Dictionaries for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MMRM	Mixed Model With Repeated Measures
MSDS	Material Safety Data Sheet
Mtb	*Mycobacterium tuberculosis*
PCI	Potential Clinical Importance
PCR	Polymerase Chain Reaction
CCI [redacted]	
PZA	Pyrazinamide
QT	Electrocardiographic QT Interval
QTc	Corrected QT Interval
RIF/RF	Rifampicin
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SoC	Standard of care
SRM	Study Reference Manual
t	Time
TB	Tuberculosis
TGA	Total Glycolytic Activity
TTP	Time to Sputum Culture Positivity
ULN	Upper Limit of Normal
WONCBP	Woman of Non-Childbearing Potential
WHO	World Health Organization
XDR	Extensively Drug Resistant

Trademark Information

Trademarks of the GSK group of companies
NONE

Trademarks not owned by the GSK group of companies
Avelon
Deltyba
Dovprela
Elturin
MedDRA
Moxibay
Rifafour e-275
Sirturo
Xpert MTB/Rif Ultra
Zyvoxid

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.9.1. Amendment 1: 05 October 2022

Overall rationale for Amendment 1

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

In participants randomised to an arm that includes GSK3036656, dolutegravir levels from PK samples may be measured if there are sufficient participants receiving dolutegravir as concomitant medication. This is to rationalise any unanticipated effects of co-administration of GSK3036656 and the ART medication, dolutegravir.

Identified in the table below are substantial changes made to the Study Protocol since the previous submitted version.

In addition, minor typographical errors and inconsistencies have been corrected and minor formatting changes have been made.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Safety Assessments; Haem/Chem/Urinalysis: Additional text clarifying that safety bloods and urine should be taken at the following visits: Screening Visit 1 (Day -9 to -3), Visit 6(Day 3) or Visit 7 (Day 4), Visit 11 (Day 8), Visit 18 (Day 15) and Visit 19 (Day 28 ±7).	Mistakenly omitted in previous version.
Section 1.3 Schedule of Activities	Safety Assessments; 12-Lead Electrocardiogram (ECG): Removal of wording from ECG assessments "For all assessments except temperature and respiratory rate". Additional wording added to clarify when triplicate ECG readings are required.	Included in previous version in error and omitted from previous version in error.
Section 1.3 Schedule of Activities	Safety Assessments; Pregnancy Test: Text updated to stipulate serum pregnancy test to be performed at the Screening Visit 1 (Day -9 to -3) and urine pregnancy test at Visits 4 (Day 1), Visit 6 or 7 (Day 3 or 4), Visit 11 (day 8), Visit 18 (Day 15 prior to discharge) and at the follow up visit* (at Day 28+7, not earlier than Day 28).	Minimisation of risk to patients and possible unborn children.
Section 1.3 Schedule of Activities	Safety Assessments; Pregnancy Test: Removal of wording "within 24 hours" prior to dosing".	Included in previous version in error.
Section 1.3 Schedule of Activities	Safety Assessments; Pregnancy Test: Removed X from Visit 12 to 16 (Day 9 to 13) and X added to Visit 11 (Day 8) and Visit 18 (Day15).	Included on Day 12 to 16 in previous version in error. Day 8 and Day 15 omitted in error.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Study Specific Assessments; Echocardiogram: Additional text added: Screening Echocardiogram may be taken on Visit 1 (Day -9 to -3), 2 (Day -2) or 3 (Day-1). Addition of X at E.D visit: "Every effort should be made to obtain Echocardiogram on participants who withdrew after Day 7 or on participants with changes in clinical status warranting a follow-up echo in the opinion of the investigator".	Omitted from previous protocol at Visit 3 in error.
Section 1.3 Schedule of Activities	Study Specific Assessments; CCI [redacted]	Included for better understanding.
Section 1.3 Schedule of Activities	Study Specific Assessments: CCI [redacted] Several instances where EVW (Early Withdrawal Visit) has been changed to E.D (Early Discontinuation).	Updated for consistency in SoA.
Section 1.3 Schedule of Activities	Urinary Delamanid Metabolites: Additional text added to clarify when 24 hour sampling should start and finish. A 24 hour urine sample will be taken on Day 1 from time of IP dose until prior to IP dose on Day 2, and on Day 14 from time of IP dose until 24 hours later. Removal of X from Day 2 to 7 and added in Day 1 to reflect this change. The following text was removed: Timings for the Day 2 and Day 14 samples should start post dose. E.g. Urine will be colleted after the administration of the Day 2 dose and will conclude 24 hours later (prior to admistration of Day 3 dose.	To provide clarification on sampling requirements

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Study Specific Assessments; Point of Care Blood Glucose: HBA1C has been removed from the procedure column.	Either random glucose testing or HBA1C may be performed as per local lab requirements.
Section 1.3 Schedule of Activities	AE/SAE/Concomitant Medications: Additional wording to clarify that Serious Adverse Events will be collected from the time a participant signs the Informed Consent.	To provide clarification on reporting requirements for SAEs.
Section 1.3 Schedule of Activities	Overnight Sputum Sampling: Removal of 15:00pm timepoint for sputum collection.	To provide flexibility in collection startime.
Section 1.3 Schedule of Activities	[redacted]	
Section 1.3 Schedule of Activities		
Section 1.3 Schedule of Activities		

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	CCI [redacted]	
Section 2.1 Study Rationale		
Section 2.3.1 Risk Assessment Table 1	Removal of wording “preliminary” from opening sentence within “Teratogenicity of GSK3036656” section.	Final data is now available
CCI [redacted]		

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design	CCI [redacted]	
Section 5.1 Inclusion Criteria	Addition of wording: ‘‘MTB/Rif Ultra®” to inclusion #2 in relation to sputum sampling.	Omitted in previous version in error.
Section 5.2 Exclusion Criteria	Addition of wording: “Participants who have previously received any of the following: GSK3036656, bedaquiline or delamanid”.	To ensure the enrolled population do not have prior exposure to study medication.
Section 6.1 Study Intervention(s) Administered	Removal of manufacturer “Aptuit” for GSK3036656 25mg capsule.	Both the 5 and 25mg capsules will be manufactured by “WuXi AppTec”.
Section 6.8 Concomitant Medication	Paracetamol/Acetaminophen, at doses of ≤4 grams/day, is permitted for use any time during the study.	Updated in line with local guidelines.

Section # and Name	Description of Change	Brief Rationale
Section 6.8 Concomitant Medication	Additional wording added: For any participants receiving concomitant dolutegravir (DTG) during the study, once participants switch to Rifafour or generic equivalent at the end of Day 14, or for those participants that are assigned to the SOC arm (i.e. Rifafour e-275 or equivalent generic alternative) once daily for 14 days, the DTG dose must be adjusted to BID as there is a drug drug interaction (with DTG as the victim and rifampicin as perpetrator) resulting in a reduction in DTG exposure.	Dolutegravir levels from PK samples may be measured in participants randomised to an arm that includes GSK3036656 and are receiving dolutegravir.
Section 7.1.2 QTc Stopping Criteria	Additional wording to clarify requirement to perform triplicate ECGs if an ECG demostrates a prolonged QT interval.	Omitted in previous version.
Section 8.2.6 Pregnancy Testing	Addition of requirement for serum pregnancy test at Screening.	Minimisation of risk to patients and possible unborn children.
CCI [redacted]		

Section # and Name	Description of Change	Brief Rationale
CCI	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
Section 8.6.4 Urinary Metabolites	Updated to provide further clarification of when testing is required.	To correct an error in previous version.
CCI [redacted]		
Section 10.2 Appendix 2 Clinical Laboratory Tests	Addition of Magnesium and Albumin to the Table 4 " Protocol-required Safety Laboratory Tests".	Omitted in previous version error.
Section 10.5 Appendix 5 Liver Safety	Addition of follow up assessments for all participants except SOC arm (previously (GSK3036656 arm only).	Increased monitoring of all participants.
Section 10.5 Appendix 5 Liver Safety	Addition of enzymatic/colorimetric assay for bilirubin or INR criteria.	Either HPLC or enzymatic/colorimetric assay is acceptable to quantify serum paracetamol concentration.
Section 10.8 Appendix 8 Abbreviations and Trademarks	Addition of MBLA to the abbreviation table.	
Section 10.9 Appendix 9 Protocol Amendment History	Addition of overall rationale for the amendment.	

10.9.2. Amendment 2: 12 January 2023

Overall rationale for Amendment 2

This study is being conducted under the ClickTB consortium, where the overall objective is to generate evidence of strong 2-drug combinations using novel and recently established antitubercular drugs. Evidence of the safety and activity of a novel TB drug candidate with an alternative mode of action to GSK3036656, BTZ-043, has recently become available. BTZ-043 inhibits the DprE-1 enzyme that is necessary to build new

cell wall glycolipopeptides during bacterial replication. BTZ-043 in combination with GSK3036656 will provide new safety and activity insights in this study.

It is anticipated that additional novel compounds may be included in this protocol in further amendments if of scientific interest and meeting the objectives of the consortium and the protocol as they are currently laid out.

Identified in the table below are substantial changes made to the Study Protocol since the previous submitted version.

In addition, minor typographical errors and inconsistencies have been corrected and minor formatting changes have been made

Section # and Name	Description of Change	Brief Rationale
Title Page	Update of the protocol title and brief title.	Updated due to inclusion of BTZ-043.
Protocol Amendment Summary of Changes Table	Update of the overall rationale of the amendment to include BTZ-043 treatment arm.	Updated due to inclusion of BTZ-043.
Section 1.1 Synopsis	Addition of text to include an additional treatment arm of GSK3036656+BTZ-043 .	To generate early bactericidal activity data, safety and tolerability data for this dual combination of 2 novel TB drug candidates in a controlled in-patient setting, prior to moving forwards into Phase 2b/c studies in outpatient settings.
Section 1.1 Synopsis	The number of participants has been increased from 55 to 70.	Sample size to reflect changes in number of participants due to inclusion of BTZ-043 arm.
Section 1.2	Schema has been updated to include 5 treatment arms	Updated to reflect changes in number of treatment arms due to inclusion of BTZ043.
Section 1.3 Schedule of Activities	Haem/Chem/Urinalysis: Addition of safety blood samples and urinalysis on day 11 for participants assigned to a treatment arm containing BTZ-043.	Updated due to inclusion of BTZ-043 for additional safety evaluations.
Section 1.3 Schedule of Activities	CCI [redacted]	

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	CCI [redacted]	
Section 1.3 Schedule of Activities		
Section 1.3 Schedule of Activities	Vital Signs: Addition of blood pressure measurements at 1h, 2h, 6h post dose for particpants assigned to BTZ-043.	Updated due to inclusion of BTZ-043 for additional safety evaluations.
Section 1.3 Schedule of Activities	CCI [redacted]	
Section 1.3 Schedule of Activities		
Section 2.1 Study Rationale	Addition of text for BTZ-043	Updated due to inclusion of BTZ-043.
Section 2.2 Background	Addition of background text for BTZ-043	Updated due to inclusion of BTZ-043.
Section 2.3.1 Risk Assessment	Addition of BTZ-043 into Table 1	Updated due to inclusion of BTZ-043.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1 Risk Assessment	Estimated creatinine clearance has been updated from ≥75 mL/min to ≥90 mL/min.	Updated due to inclusion of BTZ-043.
Section 2.3.2 Benefit Assessment	Addition of text for BTZ-043	Updated due to inclusion of BTZ-043.
Section 3 Objectives and Endpoints and/or Estimands	Addition of BTZ-043 into Objectives.	Updated due to inclusion of BTZ-043.
Section 3 Objectives and Endpoints and/or Estimands	Removal of text: "In participants randomised to an arm containing GSK3036656, DTG levels from PK samples may be measured in those participants receiving DTG as concomitant therapy."	Exclusion criteria related to antiretroviral medication have been added based on the profile of BTZ-043.
Section 3 Objectives and Endpoints and/or Estimands	CCI [redacted]	Updated due to inclusion of BTZ-043.
Section 4.1 Overall Design	Addition of text to include an additional treatment arm of GSK3036656+BTZ-043.	Updated due to inclusion of BTZ-043.

Section # and Name	Description of Change	Brief Rationale
Section 4.3 Justification for Dose	Addition of text for BTZ-043	Updated due to inclusion of BTZ-043.
Section 5.2 Exclusion Criteria	Screening criteria added of Arterial hypertension with Systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg	Updated due to inclusion of BTZ-043.
Section 5.2 Exclusion Criteria Medical Conditions	Removal of efavirenz and lopinavir boosted ritonavir as antiretroviral therapy within the last 30 days	Exclusion criteria related to antiretroviral medication have been added based on the profile of BTZ-043.
Section 5.2 Exclusion Criteria Prior/Concurrent Clinical Study Experience	Addition of text for BTZ-043.	Updated due to inclusion of BTZ-043.
Section 5.2 Exclusion Criteria Other Exclusions	Addition of criteria: "Participants unable or unwilling to adhere to study requirements"	Omitted in previous version.
Section 5.3.1 Meals and Dietary Restrictions	Addition of apple juice and orange juice to the meals and dietary restrictions	Updated due to inclusion of BTZ-043.
Section 5.3.2 Caffeine, Alcohol and Tobacco	Update to wording for caffeine restrictions.	Included for better understanding.
Section 6.1 Study Interventions Administered Table 2 and Table 3	Addition of BTZ-043	Updated due to inclusion of BTZ-043.
Section 6.3 Measures to Minimise Bias	Addition of BTZ-043	Updated due to inclusion of BTZ-043.
Section 6.7 Treatment of Overdose	Addition of BTZ-043 overdose criteria	Updated due to inclusion of BTZ-043.

Section # and Name	Description of Change	Brief Rationale
Section 6.8 Concomitant Therapy	Update to guidance for paracetamol usage for participants assigned to treatment arms containing BTZ-043, maximum 2g a day (in divided doses). Inclusion of ibuprofen 400mg, maximum 3 times per day.	Updated due to inclusion of BTZ-043.
Section 6.8 Concomitant Therapy	Concomitant Therapy: Removal of paragraph to adjust dose to BID for participants receiving concomitant medication DTG either at the end of Day 14 or participants assigned to the SOC arm.	Exclusion criteria related to antiretroviral medication have been added based on the profile of BTZ-043.
Section 8.1 Collection of Deomographic data	Added additional text to provide the rationale for the collection of sensitive information such as race and ethnicity.	To be in line with new mandatory text in the updated GSK protocol template.
Section 8.2 Microbiological Efficacy/Activity Assessments	Addition of BTZ-043 to the requirements for MIC further characterisation	Updated due to inclusion of BTZ-043.
CCI [redacted]		

Section # and Name	Description of Change	Brief Rationale
Section 9.1 Statistical Hypotheses	Addition of BTZ-043	Updated due to inclusion of BTZ-043.
Section 9.3.2 Primary Endpoint Analysis	Addition of BTZ-043	Updated due to inclusion of BTZ-043.
CCI [redacted]		
Section 9.5 Sample Size Determination	Addition of BTZ-043	Updated due to inclusion of BTZ-043.
Section 10.1.7 Data Quality Assurance	Addition of text to define the retention period of documents shared with external central reader mechanism.	To be in line with new mandatory text in the updated GSK protocol template.
Section 10.1.8 Source Documents	Addition of text to explain the actions to be taken if documents are shared externally for review by external central reader mechanism	To be in line with new mandatory text in the updated GSK protocol template.
Section 10.8 Appendix 8 Abbreviations and Trademarks	Removal of DTG from the abbreviation table.	Exclusion criteria related to antiretroviral medication have been added based on the profile of BTZ-043.

10.9.3. Amendment 3: 17 August 2023

Overall rationale for Amendment 3

This study is being conducted under the ClickTB consortium, where the overall objective is to generate evidence of strong 2-drug combinations using novel and recently established antitubercular drugs.

The previous protocol amendment described that additional compounds may be included in this protocol in further amendments if of scientific interest and meeting the objectives of the consortium and the protocol as they are currently laid out. This protocol amendment will add 3 new dual combination arms (GSK3036656+pretomanid, GSK3036656+moxifloxacin and GSK3036656 + linezolid). Evaluation of these dual combinations will complement the planned investigation of 4-drug combinations that will be studied in the Phase 2B/C UNITE4TB PARADIGM4TB study.

In addition, interim analyses will be added to the study to examine the safety, efficacy and PK data from the GSK3036656+delamanid and GSK3036656+bedaquiline arms to enable the analysis of data from these treatment arms, prior to the later completion of the other arms of the study. Data from these 2 arms would be informative for the Phase 2B/C PARADIGM4TB study that will assess the efficacy and safety of multiple GSK3036656 regimens, all of which include bedaquiline, and 3 out of 4 include delamanid.

A second interim analysis after completion of the GSK3036656 + BTZ-043 arm has been added, to inform inclusion of a 4 drug regimen containing the 2 novel compounds BTZ-043 and GSK3036656 in the Phase 2B/C UNITE4TB PARADIGM4TB study.

Furthermore, the original target of 10 SoC participants were enrolled during completion of the GSK3036656+delamanid and GSK3036656+bedaquiline arms. The SoC arm is included to ensure the results are in-line with expectations, i.e., to provide qualitative internal assay sensitivity. To ensure the results of the ongoing and new treatment arms are also in-line with expectations, an additional 13 SoC participants will be included.

Identified in the table below are substantial changes made in Protocol Amendment 3.

In addition, minor typographical errors and inconsistencies have been corrected and minor formatting changes have been made.

List of main changes in the protocol and their rationale:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Addition of text to include 3 additional treatment arms of GSK3036656+pretomanid,GSK3036656+moxifloxacin, and GSK3036656+linezolid).	To generate early bactericidal activity data, safety and tolerability data for these 3 dual combinations of GSK3036656 + licensed TB drugs in a

Section # and Name	Description of Change	Brief Rationale
		controlled in-patient setting.
Section 1.1 Synopsis	The number of participants has been increased from 70 to 128.	Sample size to reflect changes in number of participants due to inclusion of 3 additional arms plus additional SoC participants.
Section 1.2 Schema	Schema has been updated to include up to 8 treatment arms	Updated to reflect changes in number of treatment arms.
Section 1.3 Schedule of Activities	Addition of visual assessments at Screening.	Added due to the inclusion of pretomanid, linezolid and moxifloxacin.
Section 1.3 Schedule of Activities	PK Sampling: Addition of text due to inclusion of 3 additional arms.	Updated due to inclusion of pretomanid, linezolid and moxifloxacin.
Section 1.3 Overnight Sputum	Addition of wording to clarify requirements for Day 14 sample.	Added for better understanding
Section 2.1 Study Rationale	Addition of text for new treatment arms, interim analyses and additional SoC participants	Updated due to inclusion of pretomanid, linezolid and moxifloxacin.
Section 2.3.1 Risk Assessment	Addition of pretomanid, linezolid and moxifloxacin into Table 1	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 2.3.1 Risk Assessment	Addition of non clinical safety data to teratogenicity of GSK3036656.	Updated as new safety data is available.

Section # and Name	Description of Change	Brief Rationale
Section 3 Objectives and Endpoints and/or Estimands	Addition of pretomanid, linezolid and moxifloxacin into Objectives.	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 4.1 Overall Design	Addition of text to include additional treatment arms of GSK3036656+pretomanid, GSK3036656+linezolid, and GSK3036656 +moxifloxacin.	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 4.3 Justification for Dose	Addition of text for pretomanid, linezolid and moxifloxacin	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 5.2 Exclusion Criteria Prior/Concurrent Clinical Study Experience	Addition of text for pretomanid, linezolid and moxifloxacin	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 5.2 Prior/Concurrent Clinical Study Experience	Exclusion criteria has been added to exclude participants that have received moxifloxacin within 90 days of the screening visit.	Added due to inclusion of moxifloxacin
Section 5.2 Exclusion Medical Conditions	hypoalbuminemia <2.8 g/dl has been modified to <1.8 g/dl.	Exclusion criteria was specific to treatment arms containing delamanid. These treatment arms have now completed recruitment.
Section 5.2 Exclusion Medical Conditions	Exclusion criterion has been modified to exclude participants with Type 1 diabetes and participants with non-type 1 diabetes with non optimal glycemic control (HbA1c above 7%), receiving insulin injections or more than 1 glucose lowering medication.	Updated due to inclusion of pretomanid, linezolid and moxifloxacin

Section # and Name	Description of Change	Brief Rationale
	Exclusion criteria has been added to exclude diabetic participants that do not have diabetic eye screening results during the last 12 months.	
Section 5.2 Exclusion Criteria Medical Conditions	Any diseases or conditions in which there are special warnings or contrindications relating to the use of moxifloxacin have been added.	Updated due to inclusion of moxifloxacin
Section 5.2 Exclusion Criteria Medical Conditions	Exclusion criteria has been added to exclude participants with a history of ocular abnormalities, including cataracts or retinopathies.	Added due to inclusion of pretomanid, linezolid and moxifloxacin
Section 5.2 Exclusion Other exclusions	Lactose intolerance is no longer an exclusion for the study	Exclusion criteria was specific to treatment arms containing delamanid. These treatment arms have now completed recruitment.
Section 6.1 Study Interventions Administered Table 2 and Table 3	Addition of pretomanid, linezolid and moxifloxacin	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 6.3 Measures to Minimise Bias	Addition of pretomanid, linezolid and moxifloxacin	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 6.7 Treatment of Overdose	Addition of pretomanid, linezolid and moxifloxacin and overdose criteria	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 8.3.6 Visual Assessment	Visual assessments have been added to state visual acuity and colour vision will be assessed as outlined in the SoA at Screening.	Updated due to inclusion of pretomanid, linezolid and moxifloxacin

Section # and Name	Description of Change	Brief Rationale
CCI [redacted]		
Section 9.1 Statistical Hypotheses	Addition of pretomanid, linezolid and moxifloxacin	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 9.4 Interim Analysis	Addition of an interim analysis to examine the safety, efficacy and PK data from the GSK3036656+delamanid and GSK3036656+bedaquiline arms. A second Interim has been added after completion of the GSK3036656 + BTZ-043 arm.	Data from these 2 arms would be informative for the Phase 2B/C PARADIGM4 TB study
Section 9.5 Sample Size Determination	Addition of pretomanid, linezolid and moxifloxacin	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 10.3.1 Definition of AE	Addition of “visual assessments” to Events that meet AE definition.	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 10.4.2 Contreption Guidence	“Injectable” has been removed from the list of user dependant contraception methods and added to the list of low user dependant contraception methods.	This was an error in the previous protocol.
Section 10.8 Abbreviations and Trademarks	Addition of Adverse Event of Special Interest (AESI) to the abbreviation table. Addition of names to the list of Trademarks.	Updated due to inclusion of pretomanid, linezolid and moxifloxacin
Section 10.9 Appendix 9 Protocol Amendment History	Addition of overall rationale for previous amendment.	
Section 11	Addition of references to support new treatment	Updated due

Section # and Name	Description of Change	Brief Rationale
References	arms.	to inclusion of pretomanid, linezolid and moxifloxacin

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