TB Alliance

Protocol Title:	A phase 2, partially-blinded, randomised trial assessing the safety and efficacy of TBAJ876 or bedaquiline, in combination with pretomanid and linezolid in adult participants with newly diagnosed, drug-sensitive, smear-positive pulmonary tuberculosis
Protocol Number:	NC-009
Amendment Number:	Original protocol
Compound(s)/Combination:	TBAJ876 or bedaquiline (B), with pretomanid (Pa) and linezolid (L), HRZE tablets [isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E)], and HR tablets [isoniazid (H) plus rifampicin (R) combination tablets]
Trial Phase:	2
Sponsor Name:	TB Alliance
Legal Registered Address:	80 Pine Street, 20th Floor, New York, NY 10005
Regulator Agency Identifier:	TBAJ876 IND #145349
Version/Date:	Version 1.0 / 03 February 2023

PROTOCOL SIGNATURE PAGE: TB ALLIANCE

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Protocol Number:	NC-009
Protocol Date:	V1.0 dated, 03 February 2023

Signature and Date of Principal Investigator

Printed Name

Protocol Version Summary

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Original Protocol	03-February-2023

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3. PROTOCOL SUMMARY

3.1. Synopsis

Name of Sponsor: TB Alliance
Names of Investigational Products: TBAJ876, bedaquiline, pretomanid, linezolid
Title of Study: NC-009: A phase 2, partially-blinded, randomised trial assessing the safety and efficacy of TBAJ876 or bedaquiline, in combination with pretomanid and linezolid in adult participants with newly diagnosed, drug-sensitive, smear-positive pulmonary tuberculosis.
Phase of Development: 2
Treatment Indication: Pulmonary DS-TB
Study Period: Approximately 30 months (a recruitment period of at least 12 months plus 6 months of treatment (maximal duration of treatment) plus 12 months of post treatment follow-up). If a participant randomised to any of the experimental arms experiences a relapse and is kept in the study to be retreated with 2HRZE/4HR (6 months retreatment and 6 months follow up post end of retreatment), the maximum duration in the study is approximately 42 months.
Trial Objectives: The objectives of the trial are to evaluate the efficacy, safety, and tolerability of TBAJ876 (3 doses) or bedaquiline in combination with pretomanid and linezolid in adult participants with newly diagnosed, smear-positive pulmonary DS-TB in comparison to the SOC.
Trial Design and Methodology: This is a phase 2, multi-center, partially blinded, randomised clinical trial conducted in 5 treatment arms. The screening period will be up to 11 days. Participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomised in a 1:1:1:1:1 ratio using an interactive response technology that stratifies based on country and severity of disease (AFB 3+ and/or bilateral cavitation) to 1 of the 5 treatment arms: • TBAJ876 25 mg + pretomanid 200 mg + linezolid 600 mg for 8 weeks followed by HR for 7 to 18 weeks • TBAJ876 50 mg + pretomanid 200 mg + linezolid 600 mg for 8 weeks followed by HR for 7 to 18 weeks • TBAJ876 100 mg + pretomanid 200 mg + linezolid 600 mg for 8 weeks followed by HR for 7 to 18 weeks • Bedaquiline 200 mg + pretomanid 200 mg + linezolid 600 mg for 8 weeks followed by bedaquiline 100 mg + pretomanid 200 mg + linezolid 600 mg for 18 weeks • Isoniazid (H) + rifampicin (R) + pyrazinamide (Z), ethambutol (E) for 8 weeks followed by HR for 18 weeks (dose based on participant's weight). See Table 14.

Treatment Period 1 (Day 1 through 8 weeks of treatment)

TBAJ876 and bedaquiline will be blinded during the first 8 weeks of trial treatment; participants randomised to the TBAJ876 or bedaquiline arms will receive open-label pretomanid and linezolid. Participants randomised to the 2HRZE/4HR arm will receive open-label HRZE.

Treatment Period 2 (Week 9 through Week 15 or Week 26)

After receiving 8 weeks of treatment, participants randomised to the TBAJ876-Pa-L treatment arms will receive open-label HR for at least 7 weeks. Treatment completion will be allowed at Week 15 in participants randomised to the TBAJ876-Pa-L arms, if the below criteria are met:

- Week 8 or EOT Make-up Period 1 sputum MGIT culture is negative, and
- The participant has no TB-related symptoms by Week 15. Participants with symptoms that have a more likely alternative explanation are eligible to complete treatment at Week 15.

If the MGIT result is MTB positive and/or there are still TB symptom(s), participants will continue to receive HR (in the 3 TBAJ876 arms) and will complete 18 weeks of treatment with HR, for a total of 26 weeks of treatment.

After receiving 8 weeks of trial treatment, all participants randomised to the HRZE arm will receive open-label HR for 18 weeks, for a total of 26 weeks of treatment.

After receiving 8 weeks of treatment, a participants randomised to the B-Pa-L arm will receive open-label bedaquiline 100 mg (a reduction from the 200 mg daily dose in the first 8 weeks), pretomanid 200 mg, and linezolid 600 mg daily for 18 weeks, for a total of 26 weeks of trial treatment.

Follow-up Period (52 Weeks Post Treatment)

Participants in all treatment arms will complete efficacy and safety follow-up visits for 52 weeks after the end of treatment. The duration of trial participation after the ≤11-day screening period for participants in the TBAJ876-Pa-L treatment arms is expected to be 67 to 78 weeks (8-weeks Treatment Period 1, 7 to 18-weeks Treatment Period 2, and 52-weeks Follow-up Period). The duration of trial participation after the ≤11-day screening period for participants in the B-Pa-L or 2HRZE/4HR treatment arms is expected to be at least 78 weeks (8-week Treatment Period 1, 18-week Treatment Period 2, and 52-week Follow-up Period).

Dose Modification

Linezolid dose modifications (reductions and interruptions) are permitted if necessary for participant safety. Dose modifications of TBAJ876, bedaquiline, pretomanid, or HRZE are not allowed. At no time may the participant be treated with a single agent.

Full regimen interruptions will be allowed to a maximum of 14 cumulative doses during Treatment Period 1. The number of missed doses will be made up by a treatment extension starting at the end of Week 8.

The full regimen may be interrupted for up to 28 cumulative days during Treatment Period 2. The number of doses missed during Treatment Period 2 will be made up after Week 15 or Week 26 depending on the total treatment duration (see Section 7.1).

Retreatment

Participants randomised to the 3 TBAJ876-Pa-L arms and the B-Pa-L arm who relapse or experience treatment failure will be treated with 2HRZE/4HR, provided that drug susceptibility

data do not reveal emergence of resistance to HRZE or the participant has a contraindication for receiving 2HRZE/4HR, in which case they will be referred to the local NTP for further management. Participants who are re-treated will be followed for 26 weeks after the end of their re-treatment.

Treatment for HIV

Participants living with HIV will be required to be treated with dolutegravir (DTG), tenofovir (TFV), and lamivudine (3TC) combination at least during the treatment phase of the trial in participants receiving TBAJ876-Pa-L (Treatment Period 1) and B-Pa-L (Treatment Period 1 and 2). Participants randomised to the 2HRZE/4HR regimen or receiving HR during Treatment Period 2 in the TBAJ876 arms can use any ARV compatible with the regimen.

Number of Participants (Planned): The trial is planned to randomise at least 60 participants per treatment arm, for a total of at least 300 participants randomised.

Investigational Product, Dosage, and Mode of Administration:

The IMP will be supplied as the following:

- TBAJ876: 25 mg tablets
- TBAJ876 placebo for 25 mg tablets
- Bedaquiline: 100 mg tablets
- Bedaquiline placebo for 100 mg tablets
- Pretomanid: 200 mg tablets
- Linezolid: 300 mg tablets

Participants in the IMP arms will receive one of the following regimens:

Treatment Arm	**Day 1 to Week 8 (blinded)**	**Week 9 to Week 15 (open label)**	**Week 15 to Week 26 (open label)***
	Regimen	Regimen	Regimen
25 mg TBAJ876	25 mg TBAJ876, active (x 1) 25 mg TBAJ876, placebo (x 3) 200 mg Pretomanid, active (x 1) 100 mg Bedaquiline, placebo (x 2) 300 mg Linezolid, active (x 2)	HR, weight bands 1-4	HR, weight bands 1-4
50 mg TBAJ876	25 mg TBAJ876, active (x 2) 25 mg TBAJ876, placebo (x 2) 200 mg Pretomanid, active (x 1) 100 mg Bedaquiline, placebo (x 2) 300 mg Linezolid, active (x 2)	HR, weight bands 1-4	HR, weight bands 1-4
100 mg TBAJ876	25 mg TBAJ876, active (x 4) 200 mg Pretomanid, active (x 1) 100 mg Bedaquiline, placebo (x 2) 300 mg Linezolid, active (x 2)	HR, weight bands 1-4	HR, weight bands 1-4

*Only if Week 8 MGIT is MTB positive and/or participant has TB symptoms at Week 15.

B-Pa-L Day 1 to Week 8 (blinded)	**B-Pa-L Week 9 to Week 26 (open label)**
25 mg TBAJ876, placebo (x 4)	200 mg Pretomanid

200 mg Pretomanid (x 1) 100 mg Bedaquiline (x 2) 300 mg Linezolid (x 2)	100 mg Bedaquiline 300 mg Linezolid (x 2)

Instructions for dosing: All TBAJ876 and bedaquiline regimens will be administered orally once daily, to be taken with a meal and with a full glass of water (approximately 240 mL).

Control Regimen, Dosage, and Mode of Administration:

Participants in the control arm will receive open label HRZE supplied as HRZE tablets (isoniazid 75 mg plus rifampicin 150 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets) during Weeks 1 through 8.

Participants will receive HR supplied as HR tablets (isoniazid 75 mg plus rifampicin 150 mg combination tablets) during Weeks 9 through 26.

A daily supplement of Vitamin B6 will be taken with HRZE and/or HR, per each country's National TB Treatment Guideline.

The daily dose of HRZE and HR will be based on the participant's weight at screening as follows:

Weight Band	Weight Range (kg)	Number of Tablets
1	30-39	2
2	40-54	3
3	55-70	4
4	≥71	5

Instructions for dosing: HRZE/HR will be taken orally once daily with a glass of water (approximately 240 mL). HRZE/HR should not be taken with a meal (generally no closer to meals than 1 hour before or 2 hours after a meal).

Inclusion Criteria:

1. Signed written informed consent prior to undertaking any trial-related procedures.
2. Participants aged 18 to 65 years, inclusive.
3. Body weight (in light clothing and no shoes) ≥35 kg.
4. Sputum positive for tubercle bacilli (at least 1+ on the IUATLD/WHO scale on smear microscopy) at the trial laboratory.
5. DS-TB participants defined as the following:
    a. Sensitive to rifampicin and isoniazid by rapid sputum-based test (see trial Mycobacteriology Laboratory Manual) AND
    b. Either newly diagnosed for TB or have a history of being untreated for at least 3 years after cure from a previous episode of TB.
6. A chest x-ray during the screening period or within 14 days of screening which in the opinion of the investigator is compatible with pulmonary TB.
7. Be of non-childbearing potential OR using effective methods of birth control as defined below:

Non-childbearing Potential

    a. Participant is not heterosexually active or practices sexual abstinence OR
    b. Female participant or male participant's female sexual partner: bilateral oophorectomy, bilateral tubal ligation, and/or hysterectomy or has been

postmenopausal with a history of no menses for at least 12 consecutive months OR

c. Male participant or female participant's male sexual partner: vasectomized or has had a bilateral orchidectomy at least 3 months prior to screening

Effective method of birth control is defined as 1 of the following:

a. Double-barrier method which can include a combination of male condom, diaphragm, cervical cap, or female condom.

Note: Female and male condom should not be used together.

b. Combination of a barrier method with hormone-based contraceptives or an intra-uterine device.

Both male and female participants must be willing to continue practicing birth control methods and not be planning to conceive throughout treatment and for 6 months after the last dose of IMP.

References to male or female mean "assigned male or female at birth," respectively.

Exclusion Criteria:

1. History or presence of pulmonary, hepatic, musculoskeletal abnormalities, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, neurological, psychiatric disease, or any condition as determined by the investigator that could impact the participant's ability to participate in the trial.
2. Cardiovascular abnormalities such as pathological heart murmur, acute or chronic cardiac diseases including but not limited to angina (stable or unstable), acute coronary syndrome in the last 6 months, and any type of cardiomyopathy.
3. Karnofsky performance status score of <60%.
4. Abuse of alcohol or illegal drugs that in the opinion of the investigator would compromise the participant's safety or ability to follow through with all protocol specified restrictions, visits, and evaluations.
5. Historical and/or current use of local traditional medications/herbs (such as St. John's wort) which in the opinion of the investigator would compromise the participant's safety or ability to follow through with all protocol-specified restrictions, visits, and evaluations.
6. Being, or about to be, treated for malaria.
7. Is critically ill and, in the judgment of the investigator, has a diagnosis likely to result in death during the trial or the follow-up period.
8. Any evidence of extrapulmonary TB. Pleural effusion occupying <50% of hemithorax or concomitant intra- or extra-thoracic lymphadenopathy are not exclusions.
9. For participants living with HIV only:
    a. CD4+ count<200 cells/µL.
    b. WHO Clinical Stage 4 HIV disease
    c. Participants who do not agree to use DTG/TFV/3TC if ARV therapy is indicated, whilst participating in the trial and randomised to the TBAJ876 or the B-Pa-L regimen (participants randomised to the 2HRZE/4HR regimen can use any ARV compatible with the regimen).
    d. If initiation of ARV therapy is indicated within Treatment Period 1, participants who are known to be intolerant, non-responsive to DTG/TFV/3TC or have DTG/TFV/3TC as a contraindication.

10. Having participated in other clinical trials with investigational agents within 8 weeks prior to Day 1 or currently randomised in an investigational drug trial.
11. Participants with QTcF interval on ECG >450 msec at screening visit.
12. Participants with any of the following at the screening visit per medical history:
    a. A personal or family history of congenital QT prolongation.
    b. A history of known, untreated, and uncontrolled hypothyroidism.
    c. A history of or ongoing bradyarrhythmia.
    d. A history of Torsade de Pointe.
13. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycemia within the past year prior to the start of screening.
14. Females who have a positive pregnancy test during the screening visit or are already known to be pregnant, breastfeeding, or planning to conceive a child during the trial or within 6 months of completing treatment with IMP. Males planning to conceive a child during the trial or within 6 months of stopping treatment with IMP.
15. Any diseases or conditions in which the use of standard TB drugs or any of their components is contra-indicated, including but not limited to drug allergy.
16. Use of any drug within 30 days prior to randomisation known to prolong QTc interval.
17. Participants with the following toxicities at screening:
    a. Platelets <100,000/mm^3
    b. Creatinine >1.3 x ULN
    c. Haemoglobin <9.5 g/dL or <95 g/L
    d. Absolute neutrophil count <800/mm^3
    e. Serum potassium less than the lower limit of normal for the laboratory.
    f. ALT and/or AST ≥2.5 x ULN
    g. Total bilirubin ≥1.6 x ULN
    h. Direct bilirubin >1 x ULN
    i. Haemoglobin A1c ≥8.0%
    j. Total lipase ≥1.5 x ULN
    k. Total amylase ≥1.5 x ULN
    l. CPK >3 x ULN (if >3 x ULN, enquire about the participant's recent strenuous activity and consider repeating the test within the screening window)
    m. TSH >1 x ULN
    n. Positive results at screening for HBsAg, HAV IgM, or hepatitis C antibodies. Participants with positive hepatitis C antibodies but negative PCR can be allowed in the trial.

Criteria for Evaluation:

Primary Objective	**Primary Endpoint**
• To evaluate the efficacy of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, relative to 2HRZE, during 8 weeks of treatment in adult participants with newly diagnosed, smear-positive,	• Time to stable sputum culture conversion to negative status using data from weekly cultures through 8 weeks of treatment.

pulmonary DS-TB as measured by time to stable sputum culture conversion to negative status.	
Key Secondary Objective	**Key Secondary Endpoint**
• To evaluate the safety and efficacy at 26 weeks after the end of treatment of B-Pa-L relative to 2HRZE/4HR.	• Proportion of participants with a favourable outcome at 26 weeks after the end of treatment.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB, as measured by meeting the criteria to stop treatment at Week 15.	• Proportion of participants who meet the criteria to stop treatment at Week 15.
• To evaluate the safety and efficacy of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid at 26 weeks and 52 weeks after end of treatment relative to 2HRZE/4HR for the overall arms and key subgroups by stratification factors and total treatment duration.	• Proportion of participants with a favourable outcome at 26 weeks and 52 weeks after the end of treatment.
• To evaluate the safety and efficacy at 52 weeks after the end of treatment of B-Pa-L relative to 2HRZE/4HR.	• Proportion of participants with a favourable outcome at 52 weeks after the end of treatment.
• To evaluate the efficacy of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, B-Pa-L, and 2HRZE/4HR, at 26 weeks and 52 weeks after the end of treatment, as measured by relapse rates in participants that enter follow up with a favorable response at the end of treatment for the overall arms and key subgroups by stratification factors and total treatment duration.	• Relapse rates at 26 weeks and 52 weeks after the end of treatment.
• To evaluate the efficacy of B-Pa-L, relative to 2HRZE, during 8 weeks of treatment in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB as measured by time to stable sputum culture conversion to negative status.	• Time to stable sputum culture conversion to negative status using data from weekly cultures through 8 weeks of treatment.
• To assess the bactericidal activity over 2 weeks of TBAJ876 or bedaquiline in combination with pretomanid and linezolid, relative to HRZE, in adult	• BA_{TTP}(1-15) as determined by the rate of change in TTP over Days 1 to 15 of treatment, represented by the model-fitted log(TTP) as calculated by the

participants with newly diagnosed, smear-positive, pulmonary DS-TB.	regression of the observed log(TTP) counts over time.
• To assess the bactericidal activity over 8 weeks of TBAJ876 or bedaquiline in combination with pretomanid and linezolid, relative to 2HRZE, in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB.	• BA_{TTP}(1-56) as determined by the rate of change in TTP over 8 weeks of treatment, represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time.
• To evaluate stable sputum culture conversion to negative status over time during the treatment period.	• Proportion of participants with stable sputum culture conversion to negative status at Weeks 4, 6, 8, 12, 15, 20, and 26.
• To assess the safety and tolerability of the TBAJ876-Pa-L or B-Pa-L regimens at different time points, relative to 2HRZE/4HR, in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB.	• Incidence of TEAEs, by severity, drug relatedness, seriousness, leading to early discontinuation, and leading to death; and ECG, vital signs, and quantitative and qualitative clinical laboratory result measurements, changes in ophthalmic exam for visual acuity and changes noted in peripheral neuropathy, including observed and changes from baseline at Weeks 8, 26, and 26 weeks after the end of treatment.
• To evaluate the systemic exposure of TBAJ876, bedaquiline, pretomanid, and linezolid.	• Plasma concentrations of TBAJ876, bedaquiline, pretomanid, linezolid, and selected metabolites from sparse samples in all participants assigned those treatments and from an intensive profile on Day 15 in a sub-group of participants.
Exploratory Objective	**Exploratory Endpoint**
• To assess if changes in measurements of biomarker assays through the course of treatment and the post-treatment follow-up period are associated with treatment outcome.	• Change from baseline in biomarker assay through the course of treatment and the post-treatment follow-up period relative to treatment outcome.
• To correlate various endpoints measured with MGIT with AFB smear and exploratory biomarkers at Day 1 and Weeks 4, 8, 15, and 26.	• Parameters derived from modelling various endpoints measured with MGIT (e.g. MGIT negative [yes/no], quantitative outcomes) relative to AFB smear and key biomarkers of interest at Day 1 and Weeks 4, 8, 15, and 26.
• To correlate MGIT culture results at Weeks 2, 4, and 8 with favorable outcome at 26 weeks and 52 weeks after the end of treatment.	• Parameters derived from modelling MGIT culture results at Weeks 2, 4, and 8 (e.g. MGIT negative [yes/no], quantitative outcomes) relative to favourable outcome at 26 weeks and 52 weeks after the end of treatment.

• To explore predictors of MGIT negative culture at Week 8 of treatment.	• MGIT negative at Week 8 of treatment (yes/no) relative to key baseline characteristics.
• To explore the population PK and exposure-response relationships of TBAJ876, bedaquiline, pretomanid, and linezolid.	• Population-PK models, summary metrics of exposure (e.g., AUC) derived from those models, and models for relationships between exposure and efficacy and safety outcomes.
• To explore the systemic exposure of dolutegravir and tenofovir when co-administered with 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, B-Pa-L or 2HRZE.	• Trough concentrations of DTG and TFV from participants living with HIV assigned treatments.
• To explore the impact on quality of life of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, B-Pa-L, and 2HRZE/4HR.	• Time to improvement of quality of life measurements, proportion of participants with improved measurements on quality of life at different time points during and after end of treatment.

Statistical Methods:

Sample Size

At least 60 participants per arm will be sufficient to detect a hazard ratio of at least 2.0 for time to culture conversion to negative status (IMP arm vs control), with 80% power and a hazard ratio of at least 2.2 with 90% power.

Analysis Populations

The primary analysis population will be the MITT population, defined as participants who are randomised and take at least 1 dose of trial drug, without late exclusions, which are defined as:

- Lack of MTB culture positive on Day 1. Screening culture can be used to determine inclusion in MITT population if Day 1 sputum culture is contaminated or unavailable or,
- Discrepancies between screening rapid test result and corresponding culture or WGS result revealing DR-TB.

The MITT will be the primary population for all efficacy analyses.

The ITT population will include all randomised participants who took at least 1 dose of trial drug.

The PP population is the MITT population excluding participants with major protocol deviations. For the primary endpoint, the PP population will also exclude participants that received less than 7 weeks of the regimen, referred to as PP 7 weeks. For all secondary endpoints, the PP population will exclude participants that received less than 80% of trial medication, referred to as PP80.

Efficacy Analyses

The primary efficacy analysis uses a time to event approach to compare culture conversion to negative status between the investigational regimens and control regimen based on the MITT population using a stratified log rank test. Hazard ratios and corresponding 95% confidence intervals will be estimated using a stratified Cox proportional hazards model.

Statistical testing for the primary endpoint will be performed using the Hochberg method to control the overall Type I error rate at 5% for the following comparisons: TBAJ876 high dose vs. HRZE, TBAJ876 medium dose vs. HRZE, and TBAJ876 low dose vs. HRZE.

The key secondary endpoint is proportion of participants with a favorable outcome at Week 26 after the EOT based on the MITT population for B-Pa-L vs. 2HRZE/4HR. For this analysis, participants will be classified as having a favourable, unfavourable, or unassessable outcome at Week 26 after the EOT, as applicable.

A stratified analysis of the risk difference adjusting for country and severity of disease using Cochran-Mantel-Haenszel weights will be used to compare B-Pa-L with 2HRZE/4HR.

Safety Analyses

Descriptive analyses will be performed using the safety population for AE type, frequency, and severity, as well as vital sign absolute values, clinical laboratory absolute values, and physical examination findings and their respective changes from baseline for all participants who received at least 1 dose of IMP. A sample size of 60 participants per arm has a 95% probability of observing 1 or more AEs that occur at a true frequency of 5%, and a 99% probability of observing 1 or more AEs that occur at a true frequency of 10%.

3.2. Trial Flow Chart

3.2.1. Main Trial Flow Chart

Period	Screen-ing	Treatment Period 1												Treatment Period 2						Post EOT Follow-up						Early Trial Discontinuation Visit	Protocol Section
Time of Visit	**Up to 11 days before 1st IMP dose**	**Day 1**	**Day 4**	**Day 8**	**Day 11**	**Day 15**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**[1] EOT Make-up Period 1**	**Week 9**	**Week 12**	**[2] Week 15 or EOT**	**[3] Week 20**	**[3] Week 26 EOT**	**[4] EOT Make-up Period 2**	**FU Week 4**	**FU Week 8**	**FU Week 16**	**FU Week 26**	**FU Week 38**	**FU Week 52**		
Visit Window	**-11 to -1 days**		**±1 day**				**±3 days**							**±5 days**						**±14 days**							
Informed Consent	X																										13.1.3
Demography	X																										
Medical History	X																										11.3.9
Urine Drug Screen	X																										13.2
Urine Pregnancy Test	X	X						X		X		X			X			X				X			X	X	11.3.5
Urinalysis	X																										11.3.4
Exploratory Urine Sample		X						X				X				X		X									11.6
Inclusion/Exclusion	X	X																									8
Randomisation		X																									9.3
Karnofsky Assessment	X																										13.8
HIV Screening	X																										11.3.6
CD4 Count, Viral Load	X							X				X						X							X	X	11.3.6
HBsAg, Anti-Hep C Ab	X																										
Chest X-ray	X														X			X				X			X	X	11.3.7
Spot Sputum	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	11.2.1
Visual Acuity	X					X		X		X		X			X	X	X	X		X		X				X	11.3.8
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	11.3.2
Single 12-lead ECG	X																										11.3.3
Triple 12-lead ECG		X				X						X	X		X			X	X							X	11.3.3

Period	Screen-ing	Treatment Period 1												Treatment Period 2						Post EOT Follow-up						Early Trial Discontinuation Visit	Protocol Section
Time of Visit	**Up to 11 days before 1st IMP dose**	**Day 1**	**Day 4**	**Day 8**	**Day 11**	**Day 15**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**[1] EOT Make-up Period 1**	**Week 9**	**Week 12**	**[2]Week 15 or EOT**	**[3]Week 20**	**[3]Week 26 EOT**	**[4] EOT Make-up Period 2**	**FU Week 4**	**FU Week 8**	**FU Week 16**	**FU Week 26**	**FU Week 38**	**FU Week 52**		
Visit Window	**-11 to -1 days**		**±1 day**				**±3 days**							**±5 days**						**±14 days**							
[5] PK Sampling (Trial Drugs)		X		X		X	X	X	X	X	X	X	X		X			X	X							[6]X	11.5.1
[7] PK Sampling (ARV)		X		X				X				X															11.5.2
PK Sampling (24 hour)						X																					11.5.1.2
[5]Pharmacogenetic Sample		X																									12.6.1
Full Physical Exam	X	X														X		X	X								11.3.1
Height	X																										11.3.1
Cardiovascular Exam			X	X	X	X	X	X	X	X	X	X	X	X	X		X			X	X	X				X	11.3.1
Symptom Directed Exam			X	X	X	X	X	X	X	X	X	X	X	X	X		X			X	X	X	X	X	X	X	11.3.1
TB Symptoms Profile		X						X				X	X			X		X	X				X		X	X	11.2.2
Brief Peripheral Neuropathy Assessment	X					X		X		X		X	X		X	X	X	X	X			X				X	**Error! Reference source not found.**
Laboratory Safety Test	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	11.3.4
Exploratory Blood Sample		X						X				X				X		X									11.6
IMP Administration, Adherence		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								[5]X	9.1
Quality of Life Questionnaire		X														X									X	X	11.3.10

Period	Screen-ing	Treatment Period 1												Treatment Period 2						Post EOT Follow-up						Early Trial Discontinuation Visit	Protocol Section
Time of Visit	**Up to 11 days before 1st IMP dose**	**Day 1**	**Day 4**	**Day 8**	**Day 11**	**Day 15**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**[1] EOT Make-up Period 1**	**Week 9**	**Week 12**	**[2]Week 15 or EOT**	**[3]Week 20**	**[3]Week 26 EOT**	**[4] EOT Make-up Period 2**	**FU Week 4**	**FU Week 8**	**FU Week 16**	**FU Week 26**	**FU Week 38**	**FU Week 52**		
Visit Window	**-11 to -1 days**		**±1 day**				**±3 days**							**±5 days**						**±14 days**							
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.7
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	11.4

1. The EOT Make-up Period 1 visit will only be performed if the participant has missed 4 to 14 cumulative IMP doses. If less than 4 doses were missed, the participant is also required to make up those missed doses by the Week 8 visit, but there is no need to perform an additional visit prior to the transition to Treatment Period 2. See Section 9.5.2.
2. Week 15 can either be the EOT visit for participants who complete treatment at this visit in the TBAJ876-Pa-L arms or a regular visit for participants who continue treatment until Week 26. See Section 7.1 for details.
3. Visit only applicable to participants who complete treatment at Week 26.
4. The EOT Make-up Period 2 visit will only be performed if the participant has missed 6 to 28 cumulative IMP doses (during Treatment Period 2). Making up missed doses is required for participants who complete treatment at Week 15 or 26; however, the additional EOT visit is not required prior to proceeding to the Follow-up Period if less than 6 doses were missed. See Section 9.5.2.
5. Excluding participants randomised to 2HRZE/4HR.
6. IMP adherence will be assessed and PK samples will be taken only if the Early Trial Discontinuation Visit is done during either of the treatment periods and not during follow up.
7. Applies to all treatment arms; only for participants living with HIV and on ARV.

3.2.2. Re-treatment Flow Chart

Period	Re-treatment						Follow-up			Protocol Section
Time of Visit	[A]Day 1	Week 2	Week 4	Week 8	Week 16	Week 26	Week 8 after EOT	Week 16 after EOT	Week 26 after EOT	
Visit Window	±5 days						±14 days			
[B]Chest X-ray	X					X			X	11.3.7
[C]Spot Sputum	X	X	X	X	X	X	X	X	X	11.2.1
[C]Visual Acuity	X					X			X	11.3.8
Vital Signs	X	X	X	X	X	X	X	X	X	11.3.2
Height	X			X						11.3.1
Symptom Directed Exam	X	X	X	X	X	X	X	X	X	11.3.1
[C]Laboratory Safety Test	X	X	X	X	X	X				11.3.4
IMP Administration, Adherence	X	X	X	X	X	X				9.1
Concomitant Medications	X	X	X	X	X	X	X	X	X	9.7
Adverse Events	X	X	X	X	X	X	X	X	X	11.4

A: Day 1 is the day of the first dose of HRZE in participants who are retreated
B: Chest X-ray does not need to be repeated if one was performed within 4 weeks prior to Day 1.
C: Procedure does not need to be repeated if performed within 2 weeks prior to Day 1.

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
3TC	lamivudine
AE	adverse event
AESI	adverse event of special interest
AFB	acid-fast bacilli
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BA_{TTP}	bactericidal activity measured by TTP
BHZEL	bedaquiline-isoniazid-pyrazinamide-ethambutol-linezolid
BMRC	British Medical Research Council
B-Pa-L	bedaquiline, pretomanid, linezolid
bpm	beats per minute
CFR	Code of Federal Regulations
CFU	colony forming unit
C_{max}	maximum plasma concentration
CMV	cytomegalovirus
CPK	creatine phosphokinase
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Divisions of AIDS
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DR-TB	drug-resistant tuberculosis
DSMC	Data Safety Monitoring Committee
DST	drug susceptibility testing
DS-TB	drug-sensitive tuberculosis
DTG	dolutegravir

Abbreviation	Definition
EBA	early bactericidal activity
EBV	Epstein-Barr virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
EU	European Union
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus
HRZE	isoniazid, rifampicin, pyrazinamide, ethambutol
HR	isoniazid, rifampicin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IUATLD	International Union Against Tuberculosis and Lung Disease
LAM	Lipoarabinomannan
LFT	liver function test
LOAEL	lowest-observed-adverse-effect level
MAD	multiple ascending dose

Abbreviation	Definition
MAOI	monoamine oxidase inhibitor
MDR-TB	multi-drug resistant tuberculosis
MedDRA	Medical Dictionary for Regulatory Activities
MGIT	mycobacteria growth indicator tube
MIC	minimum inhibitory concentration
MITT	modified intent-to-treat
MTB	*Mycobacterium tuberculosis*
NTP	National Tuberculosis Program
OATP	organic anion transporting polypeptides
PCR	polymerase chain reaction
PD	pharmacodynamics
P-gp	P-glycoprotein
PK	pharmacokinetics
PP	per protocol
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
RR	respiratory rate
RR-TB	rifampicin-resistant tuberculosis
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SHRZ	streptomycin, isoniazid, rifampicin, pyrazinamide
SmPC	summary of product characteristics
SMQ	standardized MedDRA query
SNP	Single nucleotide polymorphism
SOC	standard of care
TB	tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TEAE	treatment-emergent adverse event
TFV	Tenofovir
TI/NR MDR-TB	treatment-intolerant/non-responsive MDR-TB

Abbreviation	Definition
TPT	TB preventive treatment
TSH	thyroid-stimulating hormone
TTP	time to positivity
ULN	upper limit of normal
USA	United States of America
WGS	whole genome sequencing
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

5. INTRODUCTION

Although some progress has been made in recent years in controlling TB globally, TB has remained a persistent problem in many countries. Tuberculosis affects an estimated 10 million people per year (range, 8.9 to 11.0 million) and is one of the world's leading infectious disease killers. Tuberculosis is responsible worldwide for an estimated 1.2 million deaths among people living without HIV (range, 1.1 to 1.3 million), and an additional 208,000 deaths among people living with HIV (range, 177,000 to 242,000) (WHO consolidated guidelines on tuberculosis, 2022).

The COVID-19 pandemic continues to have a damaging impact on access to TB diagnosis, treatment, and the burden of TB disease. Progress made in the years up to 2019 has slowed, stalled, or reversed, and global TB targets are off track. The most obvious and immediate impact was a large global drop in the reported number of people newly diagnosed with TB. From a peak of 7.1 million in 2019, only 5.8 million cases were reported in 2020 (–18%), back to the level last seen in 2012 (Global Tuberculosis Report, 2022). Reductions in the reported number of people diagnosed with TB in 2020 and 2021 suggest that the number of people with undiagnosed and untreated TB has grown, which is expected to lead to an increased number of TB deaths and community transmissions of infection. Tuberculosis incidence and mortality are projected to increase by around 5 to 15% over the next 5 years, amounting to hundreds of thousands of additional TB deaths worldwide (McQuaid et al, 2021).

Existing DS-TB treatment regimens are efficacious but lengthy in duration and involve multi-drug therapy combinations i.e., an intensive phase of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by a continuation phase of 4 months of isoniazid and rifampicin (2HRZE/4HR); this treatment regimen was first introduced as the SOC more than 40 years ago (WHO Treatment Guidelines for National TB Programs, 2022). Long and complex treatments lead to high rates of non-adherence, which often result in unfavourable outcomes, emergence of drug resistance, continued spread of disease, and increased mortality. Drug-drug interactions caused by rifampicin's potent induction of CYP enzymes are another major challenge with the 2HRZE/4HR regimen, particularly for women on hormonal contraception and TB patients co-infected with HIV taking ARVs. While a 4-month rifapentine-based regimen for treatment of pulmonary DS-TB is now recommended by the WHO as a possible alternative to 2HRZE/4HR (WHO rapid communication, 2021), there is a need for new TB drugs and drug regimens for patients with DS-TB that are efficacious, safe, well-tolerated, simpler, and that can further shorten the overall treatment duration, thereby improving adherence and favourable outcomes.

The combination of bedaquiline, a first generation diarylquinoline, with pretomanid (a nitroimidazole), and linezolid (an oxazolidinone) administered for 26 weeks has been extensively studied and is referred to as the B-Pa-L regimen. The B-Pa-L regimen demonstrated robust efficacy (>90% relapse-free cure) in adults with pulmonary XDR-TB and TI/NR MDR-TB (pre-WHO 2021 definitions) when linezolid was dosed at 1200 mg daily (Conradie et al, 2020). When the linezolid dose was decreased to 600 mg daily, efficacy was retained, and the regimen demonstrated improved tolerability (Conradie et al, 2022). B-Pa-L (plus moxifloxacin in patients with fluoroquinolone-susceptible TB) for 6 months is currently recommended for patients with DR-TB sensitive to all components of the regimen

(WHO rapid communication, 2022). The high potency of the B Pa-L regimen has potential to also shorten treatment for DS-TB (Tasneen et al, 2016).

TBAJ876 is a second generation diarylquinoline selected for development based on initial positive nonclinical results. Compared with bedaquiline, the in vitro MIC of TBAJ876 shows approximately 10-fold improvement, and in vivo TBAJ876 provides enhanced efficacy in mouse model experiments. TBAJ876 and its major M3 metabolite show a greater in vitro potency in MIC assays against diverse strains of MTB compared with bedaquiline and its M2 metabolite, including the most common bedaquiline-resistant strain Rv0678. Based on in vitro cardiac potassium channel current inhibition screening studies (hERG assay) and in vivo cardiovascular safety assessments, TBAJ876 has shown a reduced risk for QTc prolongation compared with bedaquiline. In addition, it is possible that the lower MICs over those for bedaquiline will translate into lower clinical doses which would facilitate fixed dose formulations and lower cost of goods. TBAJ876 thus has the potential to contribute both to increased efficacy and improved safety, and to a shorter TB treatment regimen for both DS-TB and DR-TB (TBAJ876 IB).

5.1. Trial Rationale

This is a phase 2, dose-ranging trial of TBAJ876 in participants with DS-TB. The bactericidal activity and safety of 3 doses of TBAJ876 (25 mg, 50 mg, and 100 mg) in combination with pretomanid 200 mg and linezolid 600 mg will be compared to the SOC (2HRZE) after 8 weeks of treatment to determine the optimal dose of TBAJ876 to carry forward in subsequent phases of development. The trial will also examine the bactericidal activity of B-Pa-L compared to 2HRZE and TBAJ876-Pa-L over 8 weeks and examine the efficacy and safety of the 26-week B-Pa-L regimen compared with the SOC (2HRZE/4HR) in participants with DS-TB.

After 8 weeks of TBAJ876-Pa-L, participants will receive HR. Participants in the TBAJ876-Pa-L arms will be allowed to complete treatment at Week 15 and enter follow up based on a negative MGIT result from a sputum sample collected at the end of Treatment Period 1 (Week 8 or EOT Make Up Period 1) as well as resolution of the participant's TB-related symptoms by Week 15. Participants with symptoms that have a more likely alternative explanation are eligible to complete treatment at Week 15. (see Section 7.1). Participants in the TBAJ876-Pa-L arms who do not meet these criteria will continue HR treatment through Week 26.

Participants in the B-Pa-L and the 2HRZE/4HR arms will receive a total of 26 weeks of treatment (6 months).

The trial will also evaluate the efficacy, in terms of relapse rate at follow-up Week 26 and Week 52 compared to the SOC arm, of 8 weeks of 25 mg, 50 mg, and 100 mg of TBAJ876-Pa-L arms (maximal total treatment duration of 26 weeks). These data will supplement the TBAJ876 dose ranging findings at Week 8 and provide insight into the optimal duration of treatment required for the TBAJ876-Pa-L regimens. All these data will support the planning for a future phase 3 trial.

Relapsing Mouse Model Data

B-Pa-L was shown to be highly effective in a BALB/c relapsing mouse model of TB based on bactericidal activity and sterilizing activity (Tasneen et al, 2016). The combination of B-Pa-L reduced the duration of treatment needed to prevent relapse in mice by >1 month compared to the first-line regimen (HRZE) and compared to B-Pa alone (Tasneen et al, 2016), indicating a significant contribution of linezolid to the efficacy of B-Pa-L. In a more recent relapsing mouse infection study (unpublished data), in which dosing of the B-Pa-L components were optimized to more closely replicate human drug exposures, B-Pa-L provided a 2.5-month improvement in the time to sterilize mouse lungs vs. the first-line HRZE comparator, even when the linezolid dose modeled a lower 600 mg QD HED (Table 1). In the same study, substituting bedaquiline with TBAJ876 (HED of 100 mg) provided an additional 1-month reduction in the treatment time required to sterilize mouse lungs, which is the same efficacy as with B-Pa-M-Z (the current efficacy benchmark for the preclinical development of future regimens). This study highlights the strong potential of B-Pa-L or TBAJ876-Pa-L to provide a shortened-duration treatment for TB forms that are sensitive to the components of the regimen.

Table 1: Relapsing Mouse Model Data (Unpublished Data)

	Months(M) of treatment prior to 3 months off treatment to assess relapse (# of mice that relapse / total # of mice)										
Regimen	M0.75	M1	M1.5	M2	M2.5	M3	M3.5	M4	M4.5	M5	M5.5
2RHZE/RH[#]	na	na	na	na	na	na	4/4	5/5	4/5	2/4	0/2
BPaL600[‡]	na	3/3	5/5	5/5	3/5	0/5	0/4	0/3	na	na	na
TBAJ876PaL600 [‡]	3/3	5/5	1/5	0/5	0/5	0/5	0/4	0/2	na	na	na
BPaMZ	na	5/5	1/5	0/6	0/5	0/4	na	na	na	na	na

R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; B = bedaquiline; Pa = pretomanid; L = linezolid; M = moxifloxacin
[#] RHZE was dosed for 2 months only followed by RH alone for the remaining periods
[‡] The linezolid dose modeled the exposure for a 600 mg *qd* human dose and was included in the regimens for the first two months, only followed by BPa or TBAJ876Pa alone for the remaining periods. B and Pa are dosed to match human exposures and TBAJ876 is dosed to match an exposure of a 100 mg human dose

5.1.1. Rationale for the Evaluation of TBAJ876 in Combination with Pretomanid and Linezolid for 8 Weeks

Traditionally, a 14-day EBA monotherapy trial would be conducted for a novel compound before its evaluation in the context of a regimen. TB Alliance considers proceeding to the evaluations of TBAJ876 as part of a regimen instead of conducting a short duration monotherapy trial to be appropriate and justified for the following reasons:

- The safety and tolerability of TBAJ876 were favourable in a healthy volunteer trial. Participants received TBAJ876 daily for a duration of 14 days at higher doses than those planned in the NC-009 trial, which produced exposures similar to those expected at the end of 8 weeks of daily dosing in the current trial (see Section 5.2.1 for additional details).
- As a congener of bedaquiline, which is approved in 70 countries (Johnson & Johnson, 2021), TBAJ876 belongs to a well-characterized class of compounds recognized for their effectiveness in the treatment of TB (WHO Class A) that has been used in the treatment of MTB-infected patients for over a decade.
- The half-life of TBAJ876 is such that steady state will not be achieved within 2 weeks of dosing. Longer monotherapy dosing may increase the risk of selection of

resistance, and as such, a longer EBA trial is not recommended. By studying TBAJ876 in the context of a longer duration combination regimen instead of short duration monotherapy, not only is the risk of selecting for MTB strains resistant to any of the components of the regimen decreased, but the data will be more relevant toward understanding the potential for developing a shortened duration treatment regimen achieving high levels of sterilizing activity and durable cures.

- The combination regimen of TBAJ876-Pa-L has precedent in terms of an approved regimen consisting of these classes (B-Pa-L). Furthermore, it represents a regimen that is likely to be developed for regulatory approval.
- The inclusion of a B-Pa-L arm in the trial allows for a direct comparison of TBAJ876 and bedaquiline, as both regimens will share the same additional components.
- The regimen of diarylquinoline-nitroimidazole-oxazolidinone for the treatment of DR-TB has been extensively studied in animals and in the clinic as the B-Pa-L regimen, providing robust data on the expected safety and efficacy profile. The substitution of a single component, bedaquiline for TBAJ876, supports the transition of TBAJ876 from phase 1 in healthy volunteers to an 8-week evaluation in the TBAJ876-Pa-L regimen.
- It is of great public health interest to accelerate development of a new diarylquinoline with a higher potential to overcome the increasing, most common bedaquiline-resistant strain Rv0678 (Ismail et al, 2022; Kaniga et al, 2022). See Section 5.2.1 for additional information.

5.1.2. Rationale for the Evaluation of a Total Treatment Duration of 15 Weeks in the TBAJ876-Pa-L Arms

Results of the recently completed TRUNCATE trial (Paton, 2022) report that a 2-month regimen of BHZEL led to relapse-free cure in about 80% of participants randomised to this treatment arm (BHZEL arm).

Shorter treatment durations have been evaluated in the past:

- Review of BMRC trials (Fox et al, 1999) shows that in participants with sputum smear-positive disease, relapse rates averaged 12% and 13% in participants treated for 4 months and 3 months, respectively. Studies were conducted from 1946 to 1986 and used several regimens not specified.
- Cochrane review of trials of standard drugs for shorter durations than 6 months (SHRZ) showed relatively higher relapse for regimens of 3 to 4 months' duration in smear-positive disease compared to 6-month treatments; however, relapse rates remained below 10%, with the exception of 1 trial where it was 18% (Gelband, 2000).
- Four-month fluoroquinolone-containing regimens (including REMOX), found overall rates of culture-confirmed relapse of 9 to 15% in a smear-positive TB population (Gillespie et al, 2014; Jindani et al, 2014; Merle et al, 2014).

- Four-month regimen with standard drugs in participants without cavitary disease and with culture conversion at 8 weeks gave a relapse rate of 7% (Johnson et al, 2009).
- Three-month and 2-month regimens with standard drugs (SHRZ) in smear-negative (culture positive) participants in Hong Kong found relapse rates of 7% and 14%, respectively (1% relapse rate in participants culture negative at baseline) (Lancet, 1979).
- Four-month rifapentine-based regimen containing moxifloxacin was non-inferior to the standard 6-month regimen in treatment of DS-TB (Dorman et al, 2021).

The evaluation of an overall shorter treatment duration with TBAJ876-Pa-L regimen for relapse rate in NC-009 is justified by:

- Comparisons of B-Pa-L and TBAJ876-Pa-L vs. HRZE show significant reductions of 1 to 2.5 months in the treatment time required to fully sterilize mice (see Table 1).
- The treatment duration required for TBAJ876-Pa-L is shorter by 1 month than that required for B-Pa-L in a relapsing mouse model (see Table 1).
- The relapsing mouse model data show a clear dose-dependent effect of TBAJ876 when used in combination with pretomanid and the 1200 mg HED for linezolid. The 25 mg, 50 mg, and 100 mg HED exposures of TBAJ876 provided equal or better activity than B-Pa-L_{1200} and significant improvement in efficacy compared to SOC HRZE/HR (see Table 1 and Table 9). Lowering the linezolid dose to 600 mg HED did not impact the sterilizing activity of the TBAJ876-Pa-L regimen; however, the 25 mg and 50 mg doses of TBAJ876 have not been tested with the 600 mg HED of linezolid.
- When considering the 50 mg and 100 mg TBAJ876 doses in combination with pretomanid and linezolid, required treatment duration is similar to the treatment duration required for B-Pa-M-Z. B-Pa-M-Z is the “gold standard” regimen that provides the shortest duration of treatment required to sterilize mice in the relapsing mouse models (see Table 1 and Table 9).
- Clinical data of B-Pa-M-Z in the SimpliciTB trial (NC-008; NCT03338621) at Week 8 showed that **84.1%** of DS-TB participants had culture converted to negative (based on 2 negative MGIT cultures at least 7 days apart) compared to 47.3% who received HRZE (unpublished data). In DS-TB participants who completed 4 months of B-Pa-M-Z (per-protocol population), **95.1%** had a favorable outcome (unpublished data). The participant population in NC-009 intends to be similar to that in SimpliciTB.

5.1.3. Rationale for the Evaluation of a 26-week B-Pa-L Regimen for Relapse Rate

In addition to allowing for a comparison of the different doses of TBAJ876 and bedaquiline during the first 8 weeks of dosing, this trial will evaluate how the B-Pa-L regimen administered for 26 weeks, as recommended in DR-TB patients, performs in a DS-TB population. Differences in baseline characteristics of the DS- and DR-TB patients and potential correlation to outcome with equally effective regimens between the 2 groups are

not well understood. Evaluating the safety and efficacy of B-Pa-L in DS-TB, combined with the data already available on B-Pa-L in DR-TB, would be valuable in the quest for a pan-TB regimen. In addition, evaluation of both B-Pa-L and 2HRZE/4HR in the same trial will provide a thorough understanding of the tolerability of B-Pa-L in comparison to 2HRZE/4HR.

5.2. Overview of Drugs in the Regimen

Background information and safety information for each compound or regimen administered in the current clinical trial is provided in this section. Comparison with the SOC 2HRZE/4HR is provided wherever possible but is often derived from separate clinical trials. While cross trial comparisons have obvious limitations, they can provide insight into the expected tolerability of B-Pa-L and TBAJ876-Pa-L in the DS-TB participant population compared to the SOC.

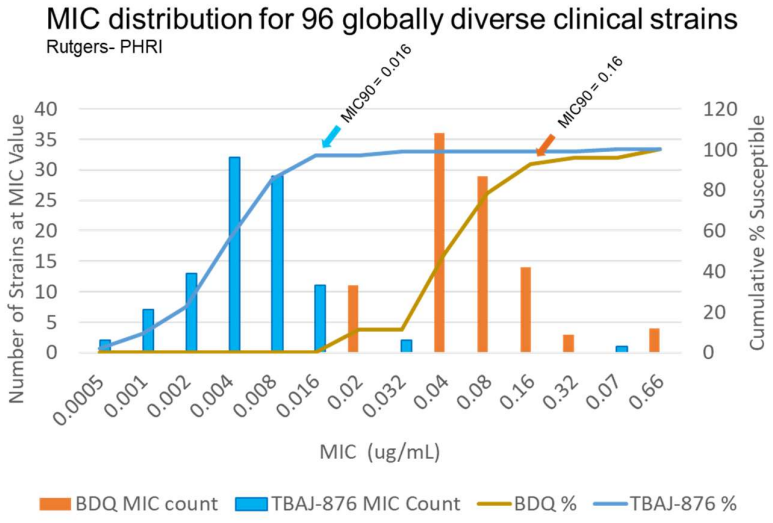
5.2.1. TBAJ876

TBAJ876 is a drug candidate derived from TB Alliance's efforts to develop a second-generation diarylquinoline with the potential to deliver superior efficacy and safety compared to bedaquiline when used as part of novel TB treatment regimens. TBAJ876 acts by inhibiting the mycobacterial ATP synthase, an enzyme essential for the generation of energy in MTB. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.

Nonclinical Data

TBAJ876 and its major M3 metabolite show greater in vitro potency in MIC assays against diverse strains of MTB compared with bedaquiline and its M2 metabolite. The MIC_{90} for TBAJ876 against a genetically diverse set of clinical strains was 0.016 mg/L vs. 0.16 mg/L for bedaquiline.

Figure 1: MIC Distribution for Diverse MTB Strains



In 2021, the WHO listed five tier 1 (*atpE*, *Rv0678*, *Rv0676c*, *Rv0677c*, and *pepQ*) and one tier 2 (*Rv1979c*) genes associated with resistance to bedaquiline (WHO Catalogue of Mutations, 2021). Variants encoding these mutations have been reported with a frequency

of 6% to 12% in clinical MTB isolates from bedaquiline-naive patients, with varying rates of phenotypic bedaquiline resistance (2.3% to 66.7%) (Rivière et al, 2022). Increasing rates of pre-existing and acquired bedaquiline resistance over time are of public health concern for which the timely availability of more robust compounds that can retain efficacy against bedaquiline-resistant strains is highly desirable (Ismail et al, 2022; Kaniga et al, 2022). TBAJ876 retained activity against strains having mutations in *Rv0678*, by far the most prevalent bedaquiline resistance mechanism observed in clinical isolates.

In mouse models of MTB, TBAJ876 demonstrated superior efficacy compared to bedaquiline, both as monotherapy and within regimens. TBAJ876 used in combination with pretomanid and linezolid (at 600 mg or 1200 mg HEDs of linezolid) provided faster sterilizing activity (by 0.5 to 1 month) than the HEDs for the B-Pa-L regimen (bedaquiline 200 mg, pretomanid 200 mg, and linezolid 600 mg), showing the potential for a shortened treatment duration (TBAJ876 IB). See Section 5.1 and Table 1 for additional details.

The target organs and processes identified in 13-week GLP-compliant toxicity studies in rats and dogs were dose and/or time-dependent (see

Table 8). All effects identified in these studies showed evidence of reversibility and occurred at exposures (mean sum of the TBAJ876 and M3 metabolite $AUC_{0\text{-}24h}$) that are 3.8 to 8.9 times the mean predicted human exposure at 100 mg TBAJ876 (the highest dose intended in the current trial; see Section 7.3.1.1 and

Table 7). Importantly, QTc prolongation was not observed with TBAJ876 in nonclinical safety pharmacology or toxicology studies (TBAJ876 IB).

Clinical Data

The TBAJ-876-CL001 trial evaluated the safety and tolerability of single (Part 1) and multiple (Part 2) ascending doses of TBAJ876 oral suspension, and single doses of 2 strengths of TBAJ876 tablets in healthy participants (Part 3). The SAD portion included 7 cohorts, and doses studied ranged from 10 to 800 mg (suspension formulation) under fasted conditions. One dose of TBAJ876, 100 mg, was also evaluated under fed conditions. The total number of participants enrolled in the SAD (Part 1 and 3) was 98, 85 treated with TBAJ876 and 13 with placebo. The duration of follow-up varied among the 7 cohorts, ranging from 28 days in the first 3 cohorts to 70 days in cohorts 4-6; cohort 7 was followed up for 14 days plus a phone call on Day 21. The MAD portion included 3 cohorts, and the doses studied ranged from 25 to 200 mg (suspension formulation) administered QD for 14 days under fed conditions. The total number of participants enrolled in the MAD part was 39, 27 randomised to active treatment and 12 to placebo. The duration of follow-up was 126 days, plus a phone call on Day 133. In Part 3, all participants (N = 30) received active treatment (single dose) and were followed up to 14 days plus a phone call on Day 21.

In both the SAD and MAD portions of the trial, the concentrations of TBAJ876 increased approximately proportionally with dose. The median terminal elimination half-life was approximately 7 weeks. Administration with food increased the AUC of TBAJ876 by approximately 60% and 90% for the single 100 mg doses of suspension and tablet formulations, respectively. The bioavailability of the tablet formulation intended for use in the present trial, under fed and fasted conditions, had similar PK to that of the oral suspension formulation.

In this trial, TBAJ876 was generally safe and well tolerated. There were no SAEs; most of the AEs were mild, and all resolved. In both the SAD and MAD portions, the AE profile was generally similar in the active and placebo groups, although the incidence of gastrointestinal AEs was numerically higher in the SAD 800 mg cohort. In the SAD portion, 2 participants (one treated with 25 mg, the other with 400 mg) experienced significant elevations in CPK, reported as rhabdomyolysis on Day 10 and 70, respectively. In both cases, participants reported mild muscle pain/discomfort after strenuous physical exertion, but there were no signs of impaired renal function, and the CPK elevations resolved within 1 and 3 weeks, respectively. In the MAD portion, 1 participant treated with TBAJ876 200 mg reported myalgia, and 2 participants reported muscle spasms, one treated with 100 mg and the other with 200 mg. These AEs occurred within 1 to 2 weeks of treatment, were not associated with changes in muscle enzymes, and resolved within 1 to 2 days. Two of 55 (4%) participants treated with TBAJ876 in the SAD portion were reported to have Grade 3 AEs of lipase elevation, as did 2 of 13 (15%) participants who received placebo. These lipase elevations were asymptomatic, did not appear to be dose related, and resolved completely. There were very few clinically significant changes in clinical laboratory tests, and all clinically significant changes resolved. There were also no reported clinically significant QT prolongations based on ECG review. One participant in the SAD portion, treated with 400 mg TBAJ876, experienced a brief episode of non-sustained ventricular tachycardia on Day 2; this participant was later discontinued from the trial due to a urine screen test positive for cocaine. Another participant in the SAD portion, treated with 400 mg, was reported to have

an AE of elevated CPK-Mb on Day 70; this was the same participant who had a significant increase in CPK on Day 70. The elevated CPK-Mb was asymptomatic, was not associated with any ECG changes, or changes in troponin I, and resolved after approximately 3 weeks. In Part 3 of the trial, the tablet formulation was also generally safe and well tolerated, with 1 participant experiencing myalgia.

The TBAJ-876-CL002 trial assessed the potential for TBAJ876 to affect the PK of substrates of CYP3A4 or P-gp. Twenty-eight subjects were enrolled and received TBAJ876 doses between 150 and 200 mg/day in both fasted and fed conditions, depending on the trial day, in such a way as to quickly reach and maintain expected clinical exposures. The trial duration was 25 days followed by a phone call on Day 32. Midazolam was used as a probe substrate for CYP3A4 interactions, and digoxin for P-gp. Interim results show that co-administration of TBAJ876 decreased the $AUC_{0\text{-}inf}$ of midazolam by 1% and C_{max} by 14%, and that co-administration of TBAJ876 increased the $AUC_{0\text{-}last}$ of digoxin by 53% and C_{max} by 18%. Based on these results, TBAJ876 does not require dose adjustments of co-administered CYP3A4 or P-gp substrates. A review of the AE data did not identify any new relevant safety findings.

5.2.2. Taken together, these nonclinical and clinical data suggest that TBAJ876 may have an advantageous efficacy and safety profile compared to bedaquiline.

Bedaquiline

Bedaquiline is a first-generation diarylquinoline and therefore shares the same mechanism of action as TBAJ876. Bedaquiline was approved in 2012 in the USA (trade name SIRTURO®) under the provisions of accelerated approval regulations as part of a combination therapy in adults and pediatric patients with pulmonary MDR-TB. Bedaquiline received conditional Marketing Authorization in the EU in 2014 and is now approved in several countries.

One safety signal associated with bedaquiline administration is QTc prolongation, as described in the package insert. Labeling notes that bedaquiline should be discontinued if the patient develops clinically significant ventricular arrhythmias or QTcF intervals of >500 msec (confirmed by repeat ECG). TB Alliance has administered bedaquiline in multiple clinical trials in several different combinations (see Section 7.3.2). In the ZeNix trial, where bedaquiline was administered with pretomanid and linezolid, 1.1% of participants had a maximum QTcF ≥500 msec, and a maximum change from baseline in QTcF >60 msec was experienced by 1.7% of DR-TB participants. In a separate trial (SimpliciTB), no participants who received 2HRZE/4HR had a maximum QTcF ≥500 msec, and 7.2% of DS-TB participants had a maximum change from baseline in QTcF >60 msec (Table 2). None of these participants had to prematurely discontinue from treatment due to the QTcF abnormalities. All the QT prolongations were asymptomatic.

Table 2: Categorical Analysis of QT Intervals: ECG Maximum QTcF Interval and Change from Baseline in ZeNix and SimpliciTB (26 Weeks of Treatment; Safety Population)

	ZeNix (B-Pa-L) DR-TB N = 181 n (%)	SimpliciTB (2HRZE/4HR) DS-TB N = 153 n (%)
Maximum QTcF (msec) ≥500	2 (1.1%)	0

Maximum change from baseline (msec) >60	3 (1.7%)	11 (7.2%)

Note: cross study comparison

Another important AE of bedaquiline (and pretomanid) is laboratory changes indicative of liver-related abnormalities. In the ZeNix trial in which bedaquiline was administered as part of the B-Pa-L regimen, 16% of DR-TB participants experienced at least 1 laboratory change indicative of liver-related abnormalities (ALT and/or AST >3 x ULN); 12.4% of DS-TB participants who received 2HRZE/4HR in a separate trial, SimpliciTB, experienced such changes (Table 3). Of note is that the percentage of participants who experienced severe liver-related laboratory abnormalities (ALT or AST >8 x ULN) was similar in the B-Pa-L and 2HRZE/4HR regimens.

Table 3: Laboratory Liver-Related Abnormalities (Safety Population)

	ZeNix (B-Pa-L) N = 181 n (%)	SimpliciTB (2HRZE/4HR) N = 153 n (%)
Total number of participants with at least one liver-related abnormality (worst elevation)	**29 (16.0%)**	**19 (12.4%)**
ALT or AST		
>3 x ULN and ≤5 x ULN	15 (8.3%)	7 (4.6%)
>5 x ULN and ≤8 x ULN	10 (5.5%)	7 (4.6%)
>8 x ULN	**4 (2.2%)**	**3 (2.0%)**
Bilirubin >2 x ULN	1 (0.6%)	2 (1.3%)
ALP >2 x ULN	0	0
ALT or AST >3 x ULN and total bilirubin >2 x ULN	1 (0.6%)	0
ALT or AST >3 x ULN and total bilirubin >2 x ULN and ALP <2 x ULN (potential Hy's law case)	1 (0.6%)	0

Note: cross study comparison

One participant in the ZeNix trial discontinued the trial after 1 week of treatment due to a severe liver laboratory abnormality. This case was confounded by prior intake of pyrazinamide, which may have contributed to the severity of the liver-related abnormality. Additionally, 1 participant met the laboratory criteria for a potential Hy's law case; however, these laboratory values were associated with the serious TEAE of hepatitis B co-infection.

The comparable tolerability of bedaquiline containing regimens and that of HRZE supports its administration to participants with DS-TB in the current trial. The bedaquiline IB and package insert provide more detailed information about bedaquiline (bedaquiline IB; Sirturo package insert).

5.2.3. Pretomanid

Pretomanid belongs to the nitroimidazole class and acts by inhibiting cell wall biosynthesis via blockage of the oxidation of hydroxymycolate to ketomycolate. Under anaerobic conditions, pretomanid causes respiratory poisoning of the bacterial cell through the release of reactive nitrogen species.

Pretomanid was approved via the Limited Population Pathway for Antibacterial and Antifungal Drugs by the USA FDA in 2019 and is indicated for administration as part of the B-Pa-L regimen for DR-TB based on Nix-TB trial data (Conradie et al, 2020). Pretomanid is also approved in EEA countries via the centralized procedure and several additional

countries. Moreover, pretomanid is pre-qualified by the WHO and currently recommended by the WHO for programmatic use in adults with pulmonary pre-XDR-TB or MDR/RR-TB (WHO rapid communication, 2022).

There is little information on pretomanid resistance prevalence. A study involving 356 clinical isolates from 6 laboratory collections identified 6 (1.7%) pretomanid-resistant mutants (Bateson et al, 2022). This number is similar to that (1.3%) reported for delamanid, another nitroimidazole drug approved for treatment of MDR-TB (Liu et al, 2018). This is not surprising as both delamanid and pretomanid are activated intracellularly through the same F_{420}-dependent pathway. Mutations in any of the 6 genes of this pathway have been associated with delamanid/pretomanid cross-resistance, although not all specific mutations confer resistance to both drugs (Lee et al, 2020).

The potential for liver enzyme elevations relative to the current SOC (2HRZE/4HR) is discussed in Section 5.2.2. The pretomanid IB and package insert provide detailed information about pretomanid (pretomanid IB; pretomanid package insert).

5.2.4. Linezolid

Linezolid is a synthetic antibacterial agent of the oxazolidinone class approved in many countries around the world for drug-resistant, gram-positive bacterial infections. The recommended dose for these infections is 600 mg twice daily for up to 28 days of therapy (Zyvox package insert). Antimicrobial effects come from inhibition of protein synthesis in the ribosomes of the infecting organism (Leach et al, 2011). Studies of the bactericidal and sterilizing activity of linezolid in a mouse model of MTB infection have demonstrated linezolid alone causes marked reductions in lung CFUs from mice following 1 to 3 months of therapy (Tasneen et al, 2016).

The use of linezolid as part of a regimen for the treatment of TB has been studied in several trials. The ZeNix trial sought to optimize linezolid dosing by treating participants with different doses (1200 mg or 600 mg) and durations (26 weeks or 9 weeks) of linezolid as part of the B-Pa-L regimen for treatment of DR-TB. Compared with dosing linezolid at 1200 mg QD, linezolid dosed at 600 mg QD, with the option to dose adjust or interrupt for the management of AEs, demonstrated robust efficacy and improved tolerability (Conradie et al, 2022).

The risk of neuropathy (peripheral and optic) and myelosuppression are discussed below in the context of 600 mg of linezolid QD for 26 weeks or 9 weeks in the ZeNix trial, in which all participants also received pretomanid and bedaquiline for 26 weeks. These observations are contextualized by describing the frequency of events reported in the 2HRZE/4HR arm of the SimpliciTB trial. The data are being presented to highlight 2 aspects of linezolid dosing:

1. Safety data based on 26 weeks of treatment at the 600 mg linezolid dose (as part of B-Pa-L) in the ZeNix trial will provide insight into the expected tolerability of the B-Pa-L regimen administered for 26 weeks in the current trial (NC-009).
2. Safety data based on 9 weeks of treatment at the 600 mg linezolid dose (as part of B-Pa-L) in the ZeNix trial will provide insight into the tolerability of the TBAJ876-Pa-L regimens in this trial in which dosing of linezolid is limited to 8 weeks.

Peripheral Neuropathy

The variety of ways in which peripheral neuropathy can be described by a participant is associated with the risk of under reporting this event if efforts are not made to account for all preferred terms associated with it. Because it may present with different symptoms, peripheral neuropathy requires grouping multiple preferred terms (using an SMQ) to ensure thorough and complete reporting. Peripheral neuropathy TEAEs described in this section are based on the SMQ for peripheral neuropathy.

In addition to linezolid, peripheral neuropathy has also been reported in association with the administration of isoniazid and ethambutol, components of the SOC for DS-TB, 2HRZE/4HR. Accepting the limitations of a cross-trial comparison,

Table 4 summarizes the frequency and grades of reported peripheral neuropathy TEAEs with the B-Pa-L and 2HRZE/4HR regimens in the ZeNix and SimpliciTB trials, respectively. Peripheral neuropathy was experienced by 24.4% and 13.3% of DR-TB participants who received linezolid 600 mg for 26 weeks and 9 weeks, respectively. In the SimpliciTB trial, 10.5% of DS-TB participants who received 2HRZE/4HR experienced peripheral neuropathy. None of these participants in either trial had to discontinue prematurely due to peripheral neuropathy TEAEs. In addition, the peripheral neuropathy TEAEs observed in the linezolid 600 mg ZeNix arms were almost exclusively mild (grade 1) in severity, while higher grade severities were more common for 2HRZE/4HR-treated participants.

Table 4: Incidence of Peripheral Neuropathy SMQ TEAEs by Severity (Safety Population)* in ZeNix and SimpliciTB (26 Weeks of Treatment)

Grade	ZeNix (B-Pa-L 600 mg/ 26 weeks) N = 45	ZeNix (B-Pa-L 600 mg/ 9 weeks) N = 45	SimpliciTB (2HRZE/4HR) N = 153
Number of participants with at least one peripheral neuropathy* TEAE	**11 (24.4%)**	**6 (13.3%)**	**16 (10.5%)**
Grade 1	10 (22.2%)	6 (13.3%)	6 (3.9%)
Grade 2	1 (2.2%)	0	9 (5.9%)
Grade 3	0	0	1 (0.6%)
Grade 4	0	0	0

*Identified using MedDRA version 23.0 SMQ
Note: cross study comparison

Optic Neuropathy

In addition to being associated with linezolid administration, optic neuropathy is associated with both isoniazid and ethambutol administration, which are components in the 2HRZE/4HR regimen. In the ZeNix trial, optic neuropathy (all preferred terms under the SMQ optic nerve disorder) was not reported in any DR-TB participant who received B-Pa-L (600 mg linezolid for 26 weeks or 9 weeks; Conradie et al, 2022); 1 case was reported by 1 participant who received 2HRZE/4HR in the SimpliciTB trial. This participant did not discontinue from the trial due to the optic neuropathy TEAE.

Myelosuppression

Linezolid administration and the SOC 2HRZE/4HR regimen have been associated with myelosuppression events. Grade 3 and grade 4 haematologic events were observed across both the B-Pa-L (ZeNix trial) and 2HRZE/4HR (SimpliciTB trial) regimens. Severe or life-threatening decreases in haemoglobin were rare. No participant who received B-Pa-L (600 mg linezolid for 26 weeks or 9 weeks) reported these events, while 3 participants (2%) who received 2HRZE/4HR in the SimpliciTB trial reported such events (

Table 5). None of these participants prematurely discontinued from the trial due to the haematology laboratory test results. Other grade 3 or 4 changes in haematologic parameters (i.e., neutrophils, leukocytes, and platelets) are provided in

Table 5; rates were similar across treatment arms and no ≥ grade 3 thrombocytopenia was reported in either trial.

Table 5: Frequency of Laboratory Test Results with a Toxicity Grade ≥3: Haematology in ZeNix and SimpliciTB (26 Weeks of Treatment) (Safety Population)

	ZeNix (B-Pa-L 600 mg/ 26 weeks) N = 45 n (%)	ZeNix (B-Pa-L 600 mg/ 9 weeks) N = 45 n (%)	SimpliciTB (2HRZE/4HR) N = 153 n (%)
Number of participants with at least one grade 3 or grade 4 haematology event (including screening and baseline)	4 (8.9%)†	6 (13.3%)	22 (14.4%)
Number of participants with at least one grade 3 or grade 4 haematology event (post baseline*)	2 (4.4%)	5 (11.1%)	17 (11.1%)
Haematology			
Haemoglobin	**0**	**0**	3 (2.0%)
Neutrophils/Leukocytes	1 (2.2%)	3 (6.7%)	6 (3.9%)
Leukocytes	1 (2.2%)	2 (4.4%)	8 (5.2%)
Platelets	0	0	0

*Post baseline is all visits after Day 1.
†1 participant had at least one grade 3/4 haematology event on Day 1. Note: cross study comparison

Tolerability-related Dose Modifications

In ZeNix, 6.7% and 8.9% of DR-TB participants who received B-Pa-L (600 mg linezolid) for 26 weeks and 9 weeks, respectively, had at least 1 linezolid dose interruption; all were due to TEAEs. The median duration of the linezolid interruption was 13 days and 12 days in the 26-week and 9-week regimens, respectively; 1 (2.2%) participant who received the 26-week regimen and 0 participants who received the 9-week regimen discontinued linezolid early. There were 8.9% and 13.3% of DR-TB participants who received B-Pa-L (600 mg linezolid) for 26 weeks and 9 weeks, respectively, who had at least 1 full B-Pa-L regimen interruption; 4.4% and 11.1% of DR-TB participants who received B-Pa-L (600 mg linezolid) for 26 weeks and 9 weeks, respectively, had full B-Pa-L regimen discontinuation.

In SimpliciTB, 18.3% of DS-TB participants who received 2HRZE/4HR had at least 1 regimen interruption (8.1% due to a TEAE) with a median duration of 6 days; 8.5% of participants had early discontinuation of the regimen and the trial (2.6% due to AE;

Table 6).

Table 6: Study Drug (Linezolid and 2HRZE/4HR) Modifications: Full Regimen (Safety Population)

	ZeNix Linezolid 600 mg 26 weeks (N = 45) n (%)	ZeNix Linezolid 600 mg 9 weeks (N = 45) n (%)	SimpliciTB 2HRZE/4HR (N = 153) n (%)
Number of participants with at least one linezolid interruption	3 (6.7%)	4 (8.9%)	
Total number of participants with linezolid discontinuations *	1 (2.2%)	0	
Total number of participants with any linezolid interruption, dose reduction or discontinuation	6 (13.3%)	6 (13.3%)	
Number of participants with at least one B-Pa-L regimen interruption	4 (8.9%)	6 (13.3%)	
Total number of participants with B-Pa-L regimen discontinuations	2 (4.4%)	5 (11.1%)	
Number of participants with at least one 2HRZE/4HR dose pause			28 (18.3%)
Total number of participants with 2HRZE/4HR discontinuation			13 (8.5%)

N = total number of participants randomised; n = number of participants in each category
* Excludes participants whose linezolid was halted as a result of being withdrawn from trial or died.

Resistance Profile of Linezolid

Resistance of MTB to linezolid in the clinic is rare, probably due to the fitness cost of resistance conferring mutations (McNeil et al, 2017). A 5-year surveillance trial conducted in 11 countries examined the susceptibility of 5036 MTB isolates; 1.5% of the tested isolates were resistant to linezolid (Kaniga et al, 2022).

Conclusions

In summary, neuropathy and myelosuppression were observed in participants who received linezolid as part of the B-Pa-L regimen and in participants who received the DS-TB SOC, 2HRZE/4HR. The adverse effects associated with linezolid can be managed effectively with monitoring and the linezolid dose modifications allowed in this trial. The linezolid and pretomanid package inserts give detailed information and recommendations for monitoring for linezolid toxicities (Zyvox package insert; pretomanid package insert). A comparison of the tolerability of linezolid-containing regimens and 2HRZE/4HR in the same trial will provide important insight into the risk-benefit of either therapeutic approach for treating DS-TB.

5.2.5. 2HRZE/4HR

The 2HRZE/4HR combination is approved, indicated, and commonly used as a 6-month treatment for DS-TB patients. Participants randomised to the 2HRZE/4HR control regimen in this trial will be given standard weight-adjusted doses of 2HRZE/4HR. See the HRZE package insert for more information (Rimstar SmPC).

5.3. Benefit:Risk Assessment

5.3.1. Risk Assessment

Potential Risk of Clinical Significance	Risk of Clinical Significance	Prevention and Mitigation Strategy
Trial Treatments		
TBAJ876: • Cardiovascular toxicity – myocardial degeneration and necrosis • QT prolongation (reduced risk of QT prolongation compared to bedaquiline) • Hepatotoxicity – transaminases increased • Skeletal muscle myopathy • Bone marrow toxicity • Pancreatitis Source: TBAJ876 IB		• Participants with QTcF >450 msec at screening are excluded. • Participants are monitored for abnormal ECG parameters and CPK (plus cardiac troponin I and myoglobin if positive) during participation in the trial. • Participants with elevated ALT or AST ≥ 2.5x ULN at screening are excluded. • Participants are monitored for liver enzyme elevations and full blood count during participation in the trial. • Participants with low hemoglobin, platelets, or neutrophils at screening are excluded. • Participants are monitored for lipase during participation in the trial. • Doses have been selected such that expected mean exposures at the high dose, 100 mg, at the end of treatment are 3.8 to 8.9 times lower than mean exposures corresponding to adverse effects observed in the 13-week toxicity studies. See Section 11.4.7.2 for further mitigation strategies.
Bedaquiline:	• Cardiovascular toxicity – (myocardial degeneration/necrosis was observed preclinically)– increased QTc interval • Hepatotoxicity – transaminases increased • Skeletal muscle myopathy • Pancreatitis Source: Bedaquiline IB	• Participants with QTcF >450 msec at screening are excluded. • Participants are monitored for abnormal ECG parameters and CPK (plus cardiac troponin I and myoglobin if positive) during participation in the trial. • Participants with elevated ALT or AST ≥ 2.5x ULN at screening are excluded.

		• Participants are monitored for liver enzyme elevations during participation in the trial. • Participants are monitored for lipase during participation in the trial See Section 11.4.7.2 for further mitigation strategies.
Pretomanid:	• Hepatotoxicity – transaminases increased Source: Pretomanid IB	• Participants with elevated ALT or AST ≥ 2.5x ULN at screening are excluded. • Participants are monitored for liver enzyme elevations during participation in the trial. See Section 11.4.7.1 for further mitigation strategies.
Linezolid:	• Myelosuppression • Peripheral neuropathy • Optic neuropathy • Lactic acidosis Source: Pretomanid IB and linezolid package insert	• Participants with low haemoglobin, platelets, or neutrophils at screening are excluded. • Full blood count is monitored during participation in the trial. • Participants with peripheral neuropathy at screening are excluded; potential development of peripheral neuropathy is monitored during trial participation. • Participants' vision is monitored using vision examinations during trial participation. • Bicarbonate/CO_2 is monitored during participation in the trial. If a participant develops signs and symptoms suggestive of lactic acidosis e.g. new onset of nausea and vomiting, extreme tiredness, trouble breathing or rapid shallow breaths, etc., lactate test should be performed by the investigator. • Linezolid is dosed at 600 mg daily which has been associated with retained efficacy but improved tolerability. Dosing may be

		dose-adjusted or interrupted for AEs of concern. See Section 11.4.7.3 for further mitigation strategies.
HRZE:	• Nervous system disorders (rifampicin) • Eye disorders (ethambutol) • Gastrointestinal disorders (rifampicin, isoniazid, pyrazinamide) • Skin and subcutaneous disorders (rifampicin) • Hepatotoxicity – liver enzymes increased (rifampicin, isoniazid, pyrazinamide) • Peripheral neuropathy (isoniazid, ethambutol) • Hyperuricemia (pyrazinamide) • Myelosuppression (isoniazid, ethambutol, and rifampicin) Source: HRZE package insert	• Participants' vision is monitored using vision examinations during trial participation. • Participants with elevated ALT or AST ≥ 2.5x ULN at screening are excluded. • Participants are monitored for liver enzyme elevations and uric acid elevations during participation in the trial. • Participants with peripheral neuropathy at screening are excluded. • Full blood count is monitored during participation in the trial.
Venipuncture (blood draws)	• Potential for bruising or infection at the site of the blood draw.	• Blood draws will be performed by trained personnel.

5.3.1.1. Risk of Treatment Failure and Relapse for the TBAJ876-Pa-L Arms

The NC-009 trial will evaluate shortened (15 week) regimens for relapse rate in participants randomised to the TBAJ876-Pa-L arms who meet pre-specified criteria to stop treatment following 8 weeks of TBAJ876-Pa-L and 7 weeks of HR. The recently reported TRUNCATE study results provide encouraging data in support of shorter treatment durations (Section 5.1), and preclinical data suggest that the sterilizing efficacy of the TBAJ876-Pa-L combination is comparable of that of the gold standard B-Pa-M-Z (Section 5.1). As such, NC-009 will provide insight into the duration of treatment required in the DS-TB participant population, informing design of future phase 3 trials (see Section 5.1). There is a potential risk that participants who receive these shortened treatments may experience a higher rate of relapse compared to the control arm. However, there are a number of mitigating factors introduced to decrease this risk:

1. Relapsing mouse model of the experimental regimens (3 doses of TBAJ876 or bedaquiline in combination with pretomanid and linezolid) shows significant reductions in the treatment time required to fully sterilize mice compared to SOC 2HRZE/4HR (see Section 5.1).
2. The criteria for completion of treatment at Week 15 is based on MGIT culture data from sputum collected at Week 8, after which participants will continue to receive

consolidation treatment with HR for 7 additional weeks until MGIT results are available. This criterion is also further strengthened by the requirement for resolution of symptoms of TB.

3. Participants who do not meet the pre-specified criteria to complete treatment at Week 15 will continue treatment for a total of 26 weeks prior to entering follow up.
4. Participants will be actively monitored for 52 weeks after completing treatment at Week 15 or at Week 26. Monitoring will include regular site visits, symptom evaluation, physical exams, chest X-ray, and sputum sample collection for mycobacteriological assessments (including MGIT) to ensure that any relapse is identified promptly.
5. Any participant identified with treatment failure or relapse will be treated with the SOC regimen (2HRZE/4HR) in the context of the NC-009 study, provided the drug susceptibility data of the infecting MTB remains sensitive to the regimen. If not, the participant will be referred to the local NTP for further management, and treating physicians will be provided with the drug susceptibility results and a medical report from the investigator.

5.3.1.2. Risk of Treatment Failure and Relapse for the 26-week B-Pa-L Arm

In the ZeNix trial, of the 45 DR-TB participants randomised to the B-Pa-L 600 mg linezolid for 26 weeks arm, 89% had a favourable outcome at 78 weeks after EOT, and there was only 1 relapse case (2.2%), with improved tolerability compared to when linezolid is dosed at 1200 mg daily. It is expected that B-Pa-L will have the same efficacy in the DS-TB population, but differences in MTB bacterial burden at baseline in DS-TB compared to DR-TB could have an impact on clinical outcomes.

Any participant identified with treatment failure or relapse will be treated with the SOC regimen (2HRZE/4HR) in the context of the NC-009 trial, provided the drug susceptibility data of the infecting MTB remains sensitive to the SOC regimen. If not, the participant will be referred to the local NTP for further management, and treating physicians will be provided with the drug susceptibility results and a medical report from the investigator.

5.3.1.3. Risk of Treatment Failure and Relapse for the Control Arm (2HRZE/4HR)

Participants will receive the SOC and will be monitored as in the other arms for treatment failure or relapse after completion of 26 weeks of treatment. In the case of treatment failure or relapse, the participant will be referred to the local NTP for further management and treating physicians will be provided with the DST results and medical report from the investigator.

5.3.2. Benefit Assessment

The main benefit to participants in this study is that they will have access to innovative drugs and regimens that may have higher rates of sterilization than the standard regimen, and thereby enable most participants to be cured after just 15 weeks of treatment in 3 out of 5 arms, with associated health economic, socioeconomic, and quality of life benefits

(Gupta et al, 2022). The 26-week regimen of B-Pa-L (linezolid 600 mg) in the ZeNix trial showed a favourable outcome of 89% in DR-TB participants, and a similar high favourable outcome in DS-TB participants is anticipated. Participants randomised to the control arm will receive the SOC treatment; as all participants in the trial, they will also benefit from the additional resources devoted to their clinical care, which will be incremental to those they could receive if they were treated in the regular clinical setting. The increased care and close monitoring may improve motivation and adherence (both are critical for good outcomes).

The close follow-up of participants during the trial should decrease the risk of harms associated with treatment failure/relapse. The costs of the treatment of TB, the laboratory monitoring, and ancillary care for the management of TB required by the protocol will be provided free of charge to the participant. This may also extend to provision of medical care for management of any complications of TB or managing the side effects of the drugs.

This trial may lead to eventual registration of a new second generation diarylquinoline, as part of a regimen, with the potential of improved potency/efficacy compared to the currently approved diarylquinoline, reduced treatment duration, potential to treat bedaquiline-resistant MTB infections, and improved tolerability.

5.3.3. Overall Benefit:Risk Conclusion

The mycobactericidal activity of TBAJ876 in nonclinical studies and the efficacy of the B-Pa-L regimen in treating participants with DR-TB argue in favor of the potential benefit of participation in this trial, as participants will receive a complete and potentially shortened treatment to which the infecting MTB are fully sensitive and that can be associated with high cure rates. The potential safety risks associated with the regimen components will be actively monitored during participation in the trial. Overall, the benefit:risk balance justifies evaluating the TBAJ876-Pa-L and B-Pa-L regimens in this trial for the treatment of participants with DS-TB.

6. OBJECTIVES AND ENDPOINTS

The objectives of the trial are to evaluate the efficacy, safety, and tolerability of TBAJ876 (3 doses), or bedaquiline, in combination with pretomanid and linezolid in adult participants with newly diagnosed smear-positive pulmonary DS-TB in comparison to the SOC.

Objectives	Endpoints
Primary	
To evaluate the efficacy of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, relative to 2HRZE, during 8 weeks of treatment in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB as measured by time to stable sputum culture conversion to negative status.	Time to stable sputum culture conversion to negative status using data from weekly cultures through 8 weeks of treatment.
Key Secondary	
To evaluate the safety and efficacy at 26 weeks after the EOT of B-Pa-L relative to 2HRZE/4HR in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB.	Proportion of participants with a favourable outcome at 26 weeks after the EOT.
Secondary	
To evaluate the efficacy of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB, as measured by meeting the criteria to stop treatment at Week 15.	Proportion of participants who meet the criteria to stop treatment at Week 15.
To evaluate the safety and efficacy of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid at 26 weeks and 52 weeks after end of treatment relative to 2HRZE/4HR for the overall arms and key subgroups by stratification factors and total treatment duration, in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB.	Proportion of participants with a favourable outcome at 26 weeks and 52 weeks after the EOT.
To evaluate the safety and efficacy at 52 weeks after the EOT of B-Pa-L relative to 2HRZE/4HR in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB.	Proportion of participants with a favourable outcome at 52 weeks after the EOT.
To evaluate the efficacy of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, B-Pa-L, and 2HRZE/4HR, at 26 weeks and 52 weeks after the EOT, as measured by relapse rates in participants that enter follow up with a favourable response at the EOT for the overall arms and key subgroups by stratification factors and total treatment duration.	Relapse rates at 26 weeks and 52 weeks after the EOT.
To evaluate the efficacy of B-Pa-L, relative to 2HRZE, during 8 weeks of treatment in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB as measured by time to stable sputum culture conversion to negative status.	Time to stable sputum culture conversion to negative status using data from weekly cultures through 8 weeks of treatment.

To assess the bactericidal activity over 2 weeks of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid or B-Pa-L, relative to 2HRZE, in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB.	BA_{TTP}(1-15) as determined by the rate of change in TTP over Days 1 to 15 of treatment, represented by the model-fitted log(TTP) as calculated by the regression of the observed log(TTP) counts over time.
To assess the bactericidal activity over 8 weeks of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid or B-Pa-L, relative to 2HRZE, in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB.	BA_{TTP}(1-56) as determined by the rate of change in TTP over 8 weeks of treatment, represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time.
To evaluate stable sputum culture conversion to negative status over time during the treatment period.	Proportion of participants with stable sputum culture conversion to negative status at Weeks 4, 6, 8, 12, 15, 20, and 26.
To assess the safety and tolerability of the 3 dose levels of TBAJ876 in combination with pretomanid and linezolid or B-Pa-L regimens at different time points, relative to 2HRZE/4HR, in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB.	Incidence of TEAEs, by severity, drug relatedness, seriousness, leading to early discontinuation, and leading to death; and ECG, vital signs, and quantitative and qualitative clinical laboratory result measurements, changes in ophthalmic exam for visual acuity and changes noted in peripheral neuropathy, including observed and changes from baseline at Weeks 8, 26, and 26 weeks after the EOT.
To evaluate the systemic exposure of TBAJ876, bedaquiline, pretomanid, and linezolid.	Plasma concentrations of TBAJ876, bedaquiline, pretomanid, linezolid, and selected metabolites from sparse samples in all participants assigned those treatments and from an intensive profile on Day 15 in a sub-group of participants.
Exploratory	
To assess if changes in measurements of biomarker assays through the course of treatment and the post-treatment follow-up period are associated with treatment outcome.	Change from baseline in biomarker assay through the course of treatment and the post-treatment follow-up period relative to treatment outcome.
To correlate various endpoints measured with MGIT with AFB smear and exploratory biomarkers at Day 1 and Weeks 4, 8, 15, and 26.	Parameters derived from modelling various endpoints measured with MGIT (e.g. MGIT negative [yes/no], quantitative outcomes) relative to AFB smear and exploratory biomarkers at Day 1 and Weeks 4, 8, 15, and 26
To correlate MGIT culture results at Weeks 2, 4, and 8 with favorable outcome at 26 weeks and 52 weeks after the EOT.	Parameters derived from modelling MGIT culture results at Weeks 2, 4, and 8 (e.g. MGIT negative [yes/no], quantitative outcomes) relative to favourable outcome at 26 weeks and 52 weeks after the EOT.
To explore predictors of MGIT negative culture at Week 8 of treatment.	MGIT negative at Week 8 of treatment (yes/no) relative to key baseline characteristics.
To explore the population PK and exposure-response relationships of TBAJ876, bedaquiline, pretomanid, and linezolid.	Population-PK models, summary metrics of exposure (e.g., AUC) derived from those models, and models for relationships between exposure and efficacy and safety outcomes.
To explore the systemic exposure of dolutegravir and tenofovir when co-administered with 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, B-Pa-L or 2HRZE.	Trough concentrations of dolutegravir and tenofovir from participants living with HIV assigned treatments.

To explore the impact on quality of life of 3 dose levels of TBAJ876 in combination with pretomanid and linezolid, B-Pa-L, and 2HRZE/4HR	Time to improvement of quality of life measurements, proportion of participants with improved measurements on quality of life at different time points during and after treatment.

7. TRIAL DESIGN

7.1. Overall Design

This is a phase 2, multi-center, partially blinded, randomised clinical trial conducted in 5 treatment arms.

The trial will be performed at multiple centers globally including, but not limited to, Georgia, the Philippines, South Africa, Tanzania, and Uganda. At least 300 participants with DS-TB who meet all of the inclusion criteria and none of the exclusion criteria, aged 18 to 65, inclusive, will be randomised to receive 1 of the 5 active treatment regimens (at least 60 participants per regimen). Participants will be randomised in a 1:1:1:1:1 ratio, using an IRT that stratifies based on country and severity of disease (AFB 3+ and/or bilateral cavitation) to 1 of the 5 daily treatment regimens after they have given written, informed consent and met all eligibility criteria.

The trial will consist of the following periods:

- Screening Period: Screening Visit up to 11 days prior to randomisation (Day 1)
- Treatment Period 1: Day 1 through Week 8 (TBAJ876-Pa-L or B-Pa-L or HRZE)
- Treatment Period 2:
    - Week 9 through Week 15 (participants in the TBAJ876-Pa-L arms that meet criteria for early completion of treatment)
    - Week 9 through Week 26 (participants in the 2HRZE/4HR or B-Pa-L arms, and participants in the TBAJ876-Pa-L arms who do not meet criteria for early completion of treatment)
- Post EOT Follow-up Period: 52 weeks after EOT

TBAJ876 and bedaquiline will be blinded during the first 8 weeks of trial treatment; participants randomised to the TBAJ876 or bedaquiline regimens will receive open-label pretomanid and linezolid for the first 8 weeks.

After receiving 8 weeks of treatment, participants in the TBAJ876-Pa-L arms and in the control arm (2HRZE/4HR) will continue treatment with HR, and participants randomised to B-Pa-L will continue treatment with B-Pa-L. Treatment completion will be allowed at Week 15 in participants randomised to the TBAJ876-Pa-L arms, if the below criteria are met*:*

- Week 8 and/or EOT Make-up Period 1 sputum MGIT culture is negative, and
- The participant has no TB-related symptoms by Week 15. Participants with symptoms that have a more likely alternative explanation are eligible to complete treatment at Week 15.As MGIT culture requires a maximum of 6 weeks incubation to confirm a negative result, all participants in the TBAJ876-Pa-L arms will receive 6 weeks of HR plus a buffer of 1 week to allow for availability of the MGIT result, hence a total of 7 weeks of HR treatment.

If the MGIT result is MTB positive and/or there are still TB symptom(s), participants will continue to receive HR (in the 3 TBAJ876-Pa-L arms) and will complete a total of 26 weeks of treatment.

Note: If Week 8 MGIT culture results are inconclusive (i.e., contamination of sputum sample), the culture sample obtained at Week 9 can be used to determine treatment duration. Incapacity to produce sputum will be considered as a negative MGIT culture result, and therefore can be used to determine participants' eligibility to complete treatment at Week 15. All participants randomised to the B-Pa-L or control arm will complete a 26-week total treatment duration.

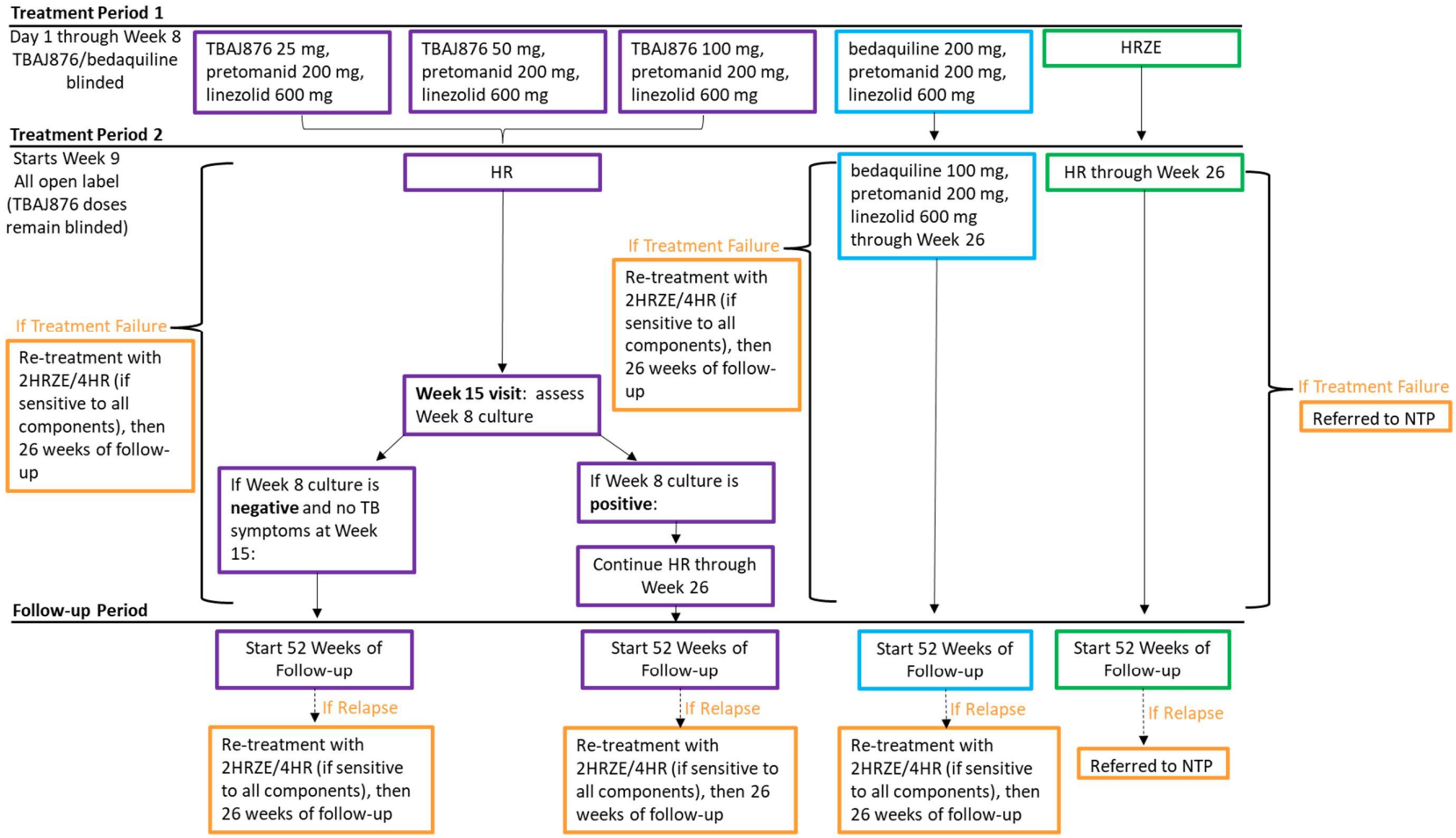
All participants will be followed for 52 weeks after the EOT.

Re-Treatment

Participants randomised to the 3 TBAJ876-Pa-L arms and B-Pa-L arm who relapse or experience treatment failure (see definition of relapse and treatment failure in Table 17) will be treated with 2HRZE/4HR, provided that drug susceptibility data do not reveal emergence of resistance or the participant has a contraindication for receiving 2HRZE/4HR, in which case they will be referred to the local NTP for further management. Participants who are re-treated will be followed for 26 weeks after the end of their re-treatment (see Figure 3, Section 5.3.1, and Section 10.1). Participants do not complete an Early Discontinuation Visit, but complete a re-treatment Day 1 visit on the day of the first dose of HRZE (see Section 3.2.2).

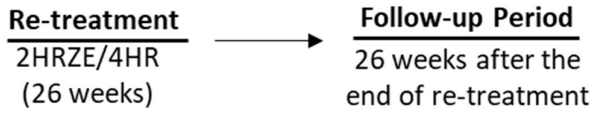
In the case of treatment failure or relapse in participants randomised to the control arm (2HRZE/4HR), the participant will be referred to the local NTP for further management, and treating physicians will be provided with the DST results and medical report from the investigator. Participants will be required to complete an Early Discontinuation Visit prior to referral to the local NTP.

Figure 2: Trial Schematic



At the Week 15 visit, the Week 8 culture and presence of TB-related symptoms will be assessed for participants who received TBAJ876-Pa-L. If the Week 8 culture is negative, and the participant has no TB-related symptoms by Week 15, the participant can complete treatment at Week 15. Participants with symptoms that have a more likely alternative explanation are eligible to complete treatment at Week 15. If the Week 8 culture is MTB positive and/or the participant has TB symptoms, the participant will continue treatment through Week 26.

Figure 3: Re-treatment Schematic



7.2. Scientific Rationale for Trial Design

The trial design has been chosen to test the superiority of 2 diarylquinoline-Pa-L regimens (TBAJ876-Pa-L and B-Pa-L) compared to 2HRZE/4HR in the DS-TB population. The primary endpoint is based on a commonly used phase 2 endpoint, time to sputum culture conversion to negative status through 8 weeks of treatment. Although B-Pa-L has proven successful in clinical trials of DR-TB participants, and nonclinical evidence suggests its treatment-shortening potential over 2HRZE/4HR, there are no B-Pa-L clinical data in DS-TB patients to date. Nonclinical evidence further suggests the superiority of TBAJ876-Pa-L over B-Pa-L in terms of treatment duration and tolerability, potentially leading to better adherence to the regimen.

The regimen of diarylquinoline-nitroimidazole-oxazolidinone for the treatment of DR-TB has been extensively studied in animals and in the clinic as the B-Pa-L regimen, providing robust data on the expected safety and efficacy profile. The substitution of a single component, bedaquiline with TBAJ876, supports the transition of TBAJ876 from phase 1 in healthy volunteers to an 8-week evaluation in the TBAJ876-Pa-L regimen. The 4 diarylquinoline-Pa-L regimens will be blinded to permit an unbiased assessment of the relative safety of the 2 diarylquinolines as well as the dose relationship of TBAJ876 safety and efficacy. Stopping a participant's treatment at Week 15 if they have a negative MGIT sputum culture result assessment by Week 8 and no TB-related symptoms (see Section 7.1) will provide insight into the optimal duration of treatment required for the TBAJ876-Pa-L regimen. See Section 5.1 for the trial rationale.

This trial will randomise participants from diverse geographic regions, including but not limited to Georgia, the Philippines, South Africa, Tanzania, and Uganda. This will help assure randomisation of participants with diverse genetic backgrounds, diverse lineages of infecting MTB, and diverse care settings to confer greater generalizability of the results.

7.3. Justification for Dose for Each Component of the Regimens

7.3.1. TBAJ876

Three different doses of TBAJ876 will be evaluated in the current trial: 25 mg, 50 mg, and 100 mg.

7.3.1.1. 100 mg as Maximum Daily Dose for 56 Days

Justification of 100 mg as the maximum daily dose is based on comparing expected exposures at 100 mg daily after 56 days with exposures seen in nonclinical toxicity studies, and by comparing predicted safety margins for TBAJ876 with corresponding values for bedaquiline, an approved diarylquinoline. Expected exposures of 100 mg daily after 56 days will be several fold lower than the LOAEL exposures in the GLP nonclinical studies.

Findings identified at the LOAEL in nonclinical studies include diarrhea, histopathologic findings of degeneration/necrosis and/or hyperplasia in the stomach mucosa, skeletal muscle myopathy (rats only), and elevated liver enzymes. Target organs identified at the LOAEL from the nonclinical toxicology studies are monitorable; clinical monitoring during the trial is detailed in Section 11.4.7.

At higher doses and/or exposures in the nonclinical toxicology studies, findings also included hepatocellular necrosis in rats, elevated amylase in dogs, effects on hematopoiesis in dogs, and myocardial degeneration and necrosis in dogs. All findings were either reversible or showed evidence of reversing after dosing was completed and are clinically monitorable.

It is suspected that the M3 metabolite as well as the parent compound contribute to the toxicities seen in the nonclinical toxicity studies, and that M3 may even be more liable for the myocardial degeneration and necrosis observed in dogs. Supporting this, in an in vitro toxicity assay with cardiomyocytes (unpublished data), the M3 metabolite of TBAJ876 impacted cell health parameters at least 10 times more potently than the parent (TBAJ876). Bedaquiline, the approved member of the diarylquinoline class, also demonstrated myocardial degeneration and necrosis in dogs. In the same in vitro assay, the M2 metabolite of bedaquiline (the structural analog to the TBAJ876 M3 metabolite) similarly impacted cell health parameters with greater potency relative to parent.

The contributory, and possibly more active, role of M3 is important, because predictions about the safety of human exposures are based on comparisons with the nonclinical species, but there are notable differences in the relative concentrations of parent and M3 between species. In the pivotal dog toxicity study, after 13 weeks of daily dosing with 15 mg/kg, the high dose at which the myocardial effects were observed, the ratio of M3 AUC to parent AUC was 4.1:1, whereas in humans, the predicted ratio after 56 days of dosing in this trial is 0.13:1. For bedaquiline, the corresponding ratios at the dog LOAEL for cardiomyocyte degeneration and necrosis and clinical ratios are 0.53:1 and 0.27:1, respectively.

Therefore, exposure comparisons between humans and the nonclinical species will consider not only the parent and M3, but also the joint contribution of both compounds via the sum of their exposures:

$$SAUC_{0\text{-}24} = AUC_{0\text{-}24,Parent} + AUC_{0\text{-}24,M3}.$$

Table 7 compares predicted exposures in humans after 56 days of dosing 100 mg QD with exposure benchmarks from the EOT in 13-week nonclinical toxicity studies. In addition to exposures at the LOAEL and NOAEL in the rat and dog studies, exposures at the high dose of the dog study are also shown, where myocardial degeneration and necrosis was observed. Also shown are the observed mean values and ranges of AUC_{0-24} after dosing 14 days at the highest dose of 200 mg in the MAD component of the TBAJ-876-CL-001 trial, which are similar to the values predicted to be achieved after 56 days of dosing 100 mg QD.

Table 7: Mean Values and Ranges of AUC_{0-24} and $SAUC_{0-24}$: Observed Nonclinical Values after 13 Weeks of Dosing in the Toxicology Studies, Observed Clinical Values after 14 Days of Dosing in the MAD Trial, and Predicted Values at 100 mg QD for 56 Days in this Trial

	AUC_{0-24} Parent (µg.h/mL)	AUC_{0-24} M3 (µg.h/mL)	$SAUC_{0-24}$ (µg.h/mL)
High dose group where myocardial degeneration and necrosis was observed (dog)	25.0 (14.4 – 39.3)	102.5 (77.6 – 155.0)	127.5 (96.5 – 194.3)
LOAEL (dog)	18.1 (11.5 – 23.5)	50.1 (32.9 – 69.2)	68.2 (45.4 – 86.9)
LOAEL (rat)*	29.6	25.4	55.0
NOAEL (dog)	10.0 (6.2 – 14.0)	17.2 (11.8 – 22.6)	27.2 (18.0 – 36.6)
NOAEL (rat)*	8.4	5.2	13.6
200 mg MAD trial (human)	12.9 (7.0 – 25.7)	1.6 (0.9 – 2.5)	14.6 (8.8 – 27.7)
Predicted 100 mg daily for 56 days in this trial	12.7 (6.8 – 20.5)	1.6 (0.9 – 2.4)	14.3 (8.0 – 22.1)

AUC_{0-24} and $SAUC_{0-24}$ values are from the end of dosing for nonclinical toxicology studies (Days 91/92) and MAD trial (Day 14) and predicted for the end of dosing in participants (8 weeks, Day 56) from a population PK model. Values shown are mean (range) of observed values for the nonclinical toxicology studies and MAD trial, and mean (5^{th} to 95^{th} percentile) of predicted values for 100 mg daily for 56 days.

*For rats, ranges are not available because AUCs were computed from 3 rats/group bled at every other time point; individual AUC values are not available.

The predicted mean $SAUC_{0-24}$ in humans after 56 days of dosing under fed conditions at 100 mg (14.3 µg.h/mL) is approximately equal to the mean $SAUC_{0-24}$ at the NOAEL dose in the rat study (13.6 µg.h/mL), 1.9 times lower than the mean $SAUC_{0-24}$ at the NOAEL dose in the dog study (27.2 µg.h/mL), and 8.9 times lower than the mean $SAUC_{0-24}$ at the high dose in the dog study where cardiomyocyte degeneration and necrosis were observed (127.5 µg.h/mL). For bedaquiline, the mean $SAUC_{0-24}$ for exposure at the dose in dogs where cardiomyocyte degeneration and necrosis were observed was 183.5 µg.h/mL, while a predicted mean clinical value after 24 weeks (the recommended treatment duration; Svensson et al, 2016) is 24.6 µg.h/mL, for a 7.5 x margin, less than the 8.9 x predicted for TBAJ876 in this trial.

Table 8 shows the ratio of SAUCs at the LOAEL of toxicity findings from 13-week nonclinical studies to predicted human exposure at 100 mg. Data show that the TBAJ876 exposures at the observed LOAELs were between 3.8 x to 8.9 x the predicted human exposure at 100 mg.

Table 8: Ratio of SAUCs at LOAEL of Finding from 13-week Nonclinical Studies to Predicted Human Exposure at 100 mg

Species	Target organ or processes	Ratio of SAUCs at LOAEL of finding from 13-week nonclinical studies to predicted human exposure at 100 mg[a]
Dog	**Heart** (cardiomyofiber necrosis/infiltrate, increased cTNI)	8.9
Rat and Dog	**Skeletal muscle** (myofiber degeneration/necrosis, increased CK, AST, ALT, K, and P)	≥3.8
Rat and Dog[b]	**Gastrointestinal** (stomach mucosal degeneration/necrosis, atrophy, and erosion [1 rat], and/or diarrhea)	≥3.8 – stomach findings ≥7.8 - diarrhea
Rat and Dog	**Liver** (Rats: single cell degeneration/necrosis and vacuolation of hepatocytes, Kupffer cell hypertrophy increased ALT/ AST; Dogs: increased liver weights, increased ALT/AST without microscopic findings)	7.8 – single cell degeneration/necrosis ≥3.8 – Kupffer cell hypertrophy and/or ↑AST/ALT
Dog	**Bone marrow** (decreased cellularity, no changes to peripheral blood cell counts)	8.9
Dog	Slight increase in amylase, no change in lipase	8.9

[a]Predicted human SAUC values at 100 mg QD for 56 days are presented in Table 7.
[b]Only observed in dogs during 2-week non-GLP toxicity study.

The mean values of $AUC_{0\text{-}24}$ and $SAUC_{0\text{-}24}$ after 14 days of dosing 200 mg QD in the MAD trial were similar to the values predicted to be achieved after 56 days of dosing 100 mg QD in this trial. As such, the cumulative safety data from TBAJ-876-CL-001 provides additional justification for the selection of 100 mg QD as the high dose of TBAJ876 to be evaluated in this trial. In TBAJ-876-CL-001, TBAJ876 was generally safe and well tolerated at all doses tested. No SAEs were reported. The AE profile was generally similar in the active and placebo groups, except for a higher incidence of musculoskeletal AEs (muscle spasms, myalgia) in participants treated with TBAJ876 in the MAD portion of the trial, and gastrointestinal AEs in the highest dose SAD cohort. Except for musculoskeletal AEs and perhaps GI AEs, the incidence of other AEs "of interest," based on nonclinical findings (cardiovascular, liver, and pancreatic), was not increased in the active groups. TBAJ-876-CL-002 also showed a favourable safety profile for TBAJ876. There were also no AEs of QT prolongation. Greater details are provided in Section 5.2.1.

Based on all of the above considerations, the highest dose of TBAJ876 100 mg daily for 56 days is expected to be acceptably safe and tolerable.

7.3.1.2. 25 mg as Minimum Daily Dose for 56 Days

Justification of 25 mg as the minimum daily dose for 56 days is based on the nonclinical data described below showing that TBAJ876 at this dose in a regimen with pretomanid and linezolid is conservatively expected to have efficacy at least similar to 2HRZE by considering exposures achieved when administered without food.

The key efficacy studies in mice supporting the selection of the low dose are relapsing mouse model studies. In these studies, 3 to 6 BALB/c mice were dosed from 0.75 to 4.5 months at 4 different doses of TBAJ876 (1.5625, 3.125, 6.25, and 12.5 mg/kg) together with pretomanid (at a dose considered pharmacokinetically similar to 200 mg QD in humans) and linezolid (at a dose considered pharmacokinetically similar to 1200 mg QD in humans). At the end of dosing, mice were left untreated for 3 months, after which they were sacrificed, and CFUs in the lung were counted. Absence of CFUs was judged to represent a cure, and presence of CFUs was judged to represent a relapse.

Table 9 shows the number of relapsing mice divided by the total number of mice in the group.

Table 9: Relapse Rates by Dose of TBAJ876, in a Regimen with Pretomanid and Linezolid (1200 mg HED) after *n* Months of Dosing in BALB/c Mice

	Relapse assessment at treatment time point in months (M); (# Relapsed mice/ # Total mice)								
Regimen	M0.75	M1	M1.5	M2	M2.5	M3	M3.5	M4	M4.5
S1PaL				3/3	5/5	3/6	0/6	0/6	0/5
S3PaL			3/3	0/5	1/6	0/6	0/6	0/6	0/5
S6.25PaL		4/4	2/6	0/6	0/6	1/4	0/3		
S12.5PaL	4/4	5/5	0/6	0/6	0/5	0/3			

S = TBAJ876; M = months of treatment
S1 = TBAJ876 25mg HED
S3 = TBAJ876 50mg HED
S6.25 = TBAJ876 100mg HED
S12.5 = TBAJ876 200mg HED

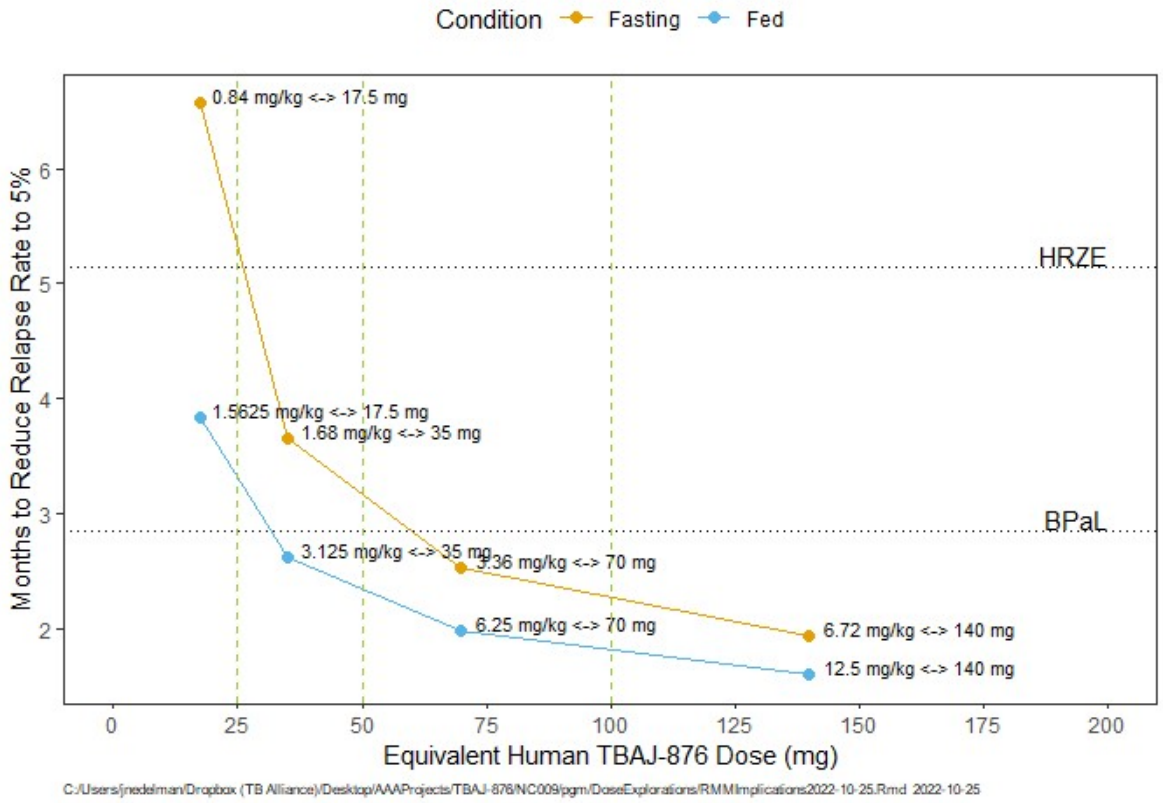
These data were analyzed by logistic regression modeling to find, for each dose of TBAJ876, the duration of dosing that reduced the rate of relapse to 5%. Then a dose-response relationship for humans was obtained by finding doses in humans that have similar exposures to the doses in mice. As was the case with toxicity, bridging mice to humans for efficacy requires consideration of both the parent and M3, because M3 is pharmacologically active, and because the M3-to-parent ratios in mice were around 1.5 to 2.0, whereas in humans (

Table 7) the ratios were around 0.15. The exposure metric used was the sum of the AUCs of parent and M3, each scaled by their respective MIC:

$$AUC_{parent}/MIC_{parent} + AUC_{M3}/MIC_{M3}$$

Figure 4 shows the resulting dose-response relationship in terms of the equivalent human doses under both fed and fasting conditions. The exposure predictions underlying the curve for the fed condition were based on the food effect seen in the SAD trial, where a high-fat, high-calorie breakfast was the meal. This may over-estimate exposures seen in clinical practice, even though taking medication with a meal will be recommended. The exposure predictions underlying the curve for the fasted condition may represent the conservative extreme.

Figure 4: Translation of the Dose-response Relationship in Mice to Dose-response Relationships in Humans by Matching on the MIC-scaled Sum of the Parent and M3 AUCs



Based on the fed-condition dose-response curve, 25 mg of TBAJ876, together with pretomanid and linezolid, is expected to be more efficacious than 2HRZE, while 50 mg and 100 mg TBAJ876 together with pretomanid and linezolid are expected to be more efficacious than B-Pa-L.

On the basis of the fasting-condition curve, 25 mg of TBAJ876 is expected to be approximately as efficacious as 2HRZE. Importantly, in NC-009 all treatment regimens will require that IMP be taken with food except the 2HRZE/4HR regimen.

Another type of mouse experiment that investigates the bactericidal activity of anti-TB drugs involves assessing the CFUs in the lungs immediately after dosing for various durations, without leaving the mice untreated before sacrifice.

In such a study, Tasneen et al compared Pa-L with HRZ after 1 and 2 months of dosing (Tasneen et al, 2016). The pretomanid and linezolid doses had similar average exposures to 200 mg QD and 1200 mg QD, respectively, in humans. For HRZ, the mean (± SD) $\log_{10}$ CFU counts were 3.47 ± 0.37 and 1.59 ± 0.25 after 1 and 2 months, respectively. For Pa-L, the corresponding values were 3.23 ± 0.41 and 1.48 ± 0.12, respectively. These results suggest that, at least over a dosing duration of 2 months, even Pa-L without the addition of TBAJ876 may be about as efficacious as 2HRZE. Barring any antagonism, the addition of 25 mg TBAJ876 would therefore comprise an acceptable dose and duration.

7.3.2. Bedaquiline

Bedaquiline is currently registered in many countries to be administered to patients with pulmonary TB by the following scheme: 400 mg QD for Days 1 through 14 followed by 200 mg 3 times per week for the remainder of treatment. In this trial, bedaquiline will be administered as 200 mg QD for 8 weeks, followed by 100 mg QD for the remaining 18 weeks. This daily dosing scheme allows a more convenient dosing that should ultimately enhance participant adherence and may allow the development of fixed dose combinations with other drugs.

This daily dosing regimen is supported by safety and efficacy demonstrated in the ZeNix trial that followed the same bedaquiline dosing regimen (Conradie et al, 2022), the NC-005 trial that administered bedaquiline 200 mg daily over 8 weeks (Tweed et al, 2019), and by PK modelling and simulation of the daily dosing scheme (Salinger et al, 2019).

7.3.3. Pretomanid

The dose of pretomanid is 200 mg QD, the dose approved by the USA FDA and the EMA for use in the B-Pa-L regimen (pretomanid package insert; pretomanid doveprela SmPC).

7.3.4. Linezolid

Linezolid in combination with a diarylquinoline and pretomanid has been shown to allow substantial shortening of treatment duration, relative to HRZE, and to prevent relapse in mouse studies (see Section 5.1). While the pretomanid USA FDA package insert and EMA SmPC indicate the linezolid dose as part of the B-Pa-L regimen is 1200 mg QD, the dose of linezolid in this trial is 600 mg QD.

Recent results from the ZeNix trial show that the safety profile of linezolid administered at 600 mg QD in combination with bedaquiline and pretomanid is significantly improved over that of 1200 mg QD while maintaining high efficacy. This is corroborated by similar safety findings in the TB Practecal trial in which linezolid was administered at 600 mg for 4 months followed by 300 mg for 2 months. Based on these studies, B-Pa-L with linezolid dosed 600 mg QD is recommended by the WHO for treatment of DR-TB that is sensitive to all components of the regimen (WHO rapid communication, 2022).

7.3.5. 2HRZE/4HR

The 2HRZE/4HR combination tablets are approved, indicated, and commonly used as a 6-month treatment for DS-TB patients. Participants randomised to the 2HRZE/4HR control regimen in this trial will be given standard weight-adjusted doses of 2HRZE/4HR.

8. TRIAL POPULATION

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

8.1. Inclusion Criteria

Participants are required to meet all the following inclusion criteria during the screening period to be randomised.

1. Signed written informed consent prior to undertaking any trial-related procedures.
2. Participants aged 18 to 65 years, inclusive.
3. Body weight (in light clothing and no shoes) ≥35 kg.
4. Sputum positive for tubercle bacilli (at least 1+ on the IUATLD/WHO scale [Section 13.4] on smear microscopy) at the trial laboratory.
5. DS-TB participants defined as the following:
   a. Sensitive to rifampicin and isoniazid by rapid sputum-based test (see trial Mycobacteriology Laboratory Manual) AND
   b. Either newly diagnosed for TB or have a history of being untreated for at least 3 years after cure from a previous episode of TB.
6. A chest x-ray during the screening period or within 14 days of screening which in the opinion of the investigator is compatible with pulmonary TB.
7. Be of non-childbearing potential OR using effective methods of birth control as defined below:

   Non-childbearing Potential
   a. Participant is not heterosexually active or practices sexual abstinence OR
   b. Female participant or male participant's female sexual partner: bilateral oophorectomy, bilateral tubal ligation, and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months OR
   c. Male participant or female participant's male sexual partner: vasectomized or has had a bilateral orchidectomy at least 3 months prior to screening.

   Effective method of birth control is defined as one of the following:
   d. Double-barrier method, which can include a combination of male condom, diaphragm, cervical cap, or female condom.
      Note: Female and male condom should not be used together.
   e. Combination of a barrier method with hormone-based contraceptives or an intra-uterine device.

   Both male and female participants must be willing to continue practicing birth control methods and not be planning to conceive throughout treatment and for 6 months after the last dose of IMP.

   References to male or female mean "assigned male or female at birth," respectively.

8.2. Exclusion Criteria

Participants will be excluded from participating in the trial if they meet any of the following criteria during the screening period:

1. History or presence of pulmonary, hepatic, musculoskeletal abnormalities, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, neurological, psychiatric disease, or any condition as determined by the investigator that could impact the participant's ability to participate in the trial.
2. Cardiovascular abnormalities, such as pathological heart murmur, acute or chronic cardiac diseases including but not limited to angina (stable or unstable), acute coronary syndrome in the last 6 months, and any type of cardiomyopathy.
3. Karnofsky performance status score of <60% (Section 13.8).
4. Abuse of alcohol or illegal drugs that in the opinion of the investigator would compromise the participant's safety or ability to follow through with all protocol-specified restrictions, visits, and evaluations.
5. Historical and/or current use of local traditional medications/herbs (such as St. John's wort) which in the opinion of the investigator would compromise the participant's safety or ability to follow through with all protocol-specified restrictions, visits, and evaluations.
6. Being, or about to be, treated for malaria.
7. Is critically ill and, in the judgment of the investigator, has a diagnosis likely to result in death during the trial or the follow-up period.
8. Any evidence of extrapulmonary TB. Pleural effusion occupying <50% of hemithorax or concomitant intra- or extra-thoracic lymphadenopathy are not exclusions.
9. For participants living with HIV only:
    a. CD4+ count <200 cells/µL.
    b. WHO Clinical Stage 4 HIV disease (Section 13.5).
    c. Participants who do not agree to use DTG/TFV/3TC if ARV therapy is indicated, whilst participating in the trial and are randomised to the TBAJ876 or the B-Pa-L regimen (participants randomised to the 2HRZE/4HR regimen can use any ARV compatible with the regimen).
    d. If initiation of ARV therapy is indicated within Treatment Period 1, participants who are known to be intolerant, non-responsive to DTG/TFV/3TC or have DTG/TFV/3TC as a contraindication.
10. Having participated in other clinical trials with investigational agents within 8 weeks prior to Day 1 or currently randomised in an investigational drug trial.
11. Participants with QTcF interval >450 msec at screening based on ECG measurement.
12. Participants with any of the following at the screening visit per medical history:
    a. A personal or family history of congenital QT prolongation.
    b. A history of known, untreated, and uncontrolled hypothyroidism.
    c. A history of or ongoing bradyarrhythmia.

d. A history of Torsade de Pointe.

13. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycemia within the past year prior to the start of screening.
14. Females who have a positive pregnancy test during the screening visit or are already known to be pregnant, breastfeeding, or planning to conceive a child during the trial or within 6 months of completing treatment with IMP. Males planning to conceive a child during the trial or within 6 months of stopping treatment with IMP.
15. Any diseases or conditions in which the use of standard TB drugs or any of their components is contraindicated, including but not limited to drug allergy.
16. Use of any drug within 30 days prior to randomisation known to prolong QTc interval (see Section 9.7 for a list of medications).
17. Participants with the following toxicities at screening:
    a. Platelets <100,000/mm^3
    b. Creatinine >1.3 x ULN
    c. Haemoglobin <9.5 g/dL or <95 g/L
    d. Absolute neutrophil count <800/mm^3
    e. Serum potassium less than the lower limit of normal for the laboratory.
    f. ALT and/or AST ≥2.5 x ULN
    g. Total bilirubin ≥1.6 x ULN
    h. Direct bilirubin >1 x ULN
    i. Haemoglobin A1c ≥8.0%
    j. Total lipase ≥1.5 x ULN
    k. Total amylase ≥1.5 x ULN
    l. CPK >3 x ULN (if >3 x ULN, enquire about the participant's recent strenuous activity and consider repeating the test within the screening window)
    m. TSH >1 x ULN
    n. Positive results at screening for HBsAg, HAV IgM, or hepatitis C antibodies. Participants with positive hepatitis C antibodies but negative PCR can be allowed in the trial.

8.3. Lifestyle Considerations

Contraception requirements during participation in the trial are provided in Exclusion Criterion 7.

8.3.1. Meals and Dietary Restrictions

Tyramine is an amino acid that helps regulate blood pressure. Monoamine oxidase inhibitors (MAOIs) block an enzyme known as monoamine oxidase, which is important for breaking down excess tyramine in the body. Linezolid is considered a reversible inhibitor of monoamine oxidase. To avoid a sudden and dangerous increase in blood pressure, large quantities of foods or beverages with high tyramine content should be avoided while taking linezolid. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 0.5 mg

tyramine per gram), fermented or air-dried meats (0.004 to 0.28 mg tyramine per gram), sauerkraut (0.035 mg tyramine per gram), and soy sauce (5 mg tyramine per 1 teaspoon). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.

Instructions for dosing of IMP in relation to meals are provided in Section 9.1.

8.3.2. Alcohol

Alcohol should be avoided while taking IMP.

8.4. Screen Failures

Screen failures are defined as participants who provided written informed consent but who were not randomised.

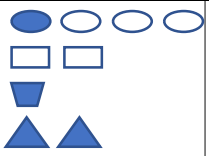
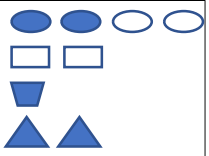
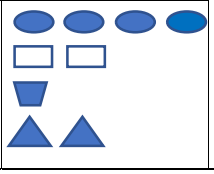
9. INVESTIGATIONAL MEDICINAL PRODUCT AND CONCOMITANT THERAPY

9.1. IMP Administration

Table 10: IMP

IMP name	• Regimen of TBAJ876 + pretomanid + linezolid for 8 weeks, followed by HR for 7 to 18 weeks • Regimen of bedaquiline + pretomanid + linezolid for 26 weeks • Regimen of HRZE/HR for 26 weeks
Route of administration	Oral
Use	Investigational
Sourcing	Provided centrally by the TB Alliance

Table 11: Investigational Regimens

Day 1 to Week 8 *QD for 8 weeks*			**Week 9 to Week 15** *QD for 7 weeks**			**Week 15 to Week 26** ***if MGIT Positive and/or with TB symptoms****		
Blinding	Regimen	Number of tablets	Blinding	Regimen	Number of tablets	Blinding	Regimen	Number of tablets
☐ Open label ☒ Blinded	TBAJ876 **25 mg** Pa-L		☒ Open label ☐ Blinded	HR	Up to 5 tablets *(per weight band)*	☒ Open label ☐ Blinded	HR	Up to 5 tablets *(per weight band)*
	TBAJ876 **50 mg** Pa-L							
	TBAJ876 **100 mg** Pa-L							

*See Section 7.1 for a description of HR dosing.

Table 12: B-Pa-L Regimen

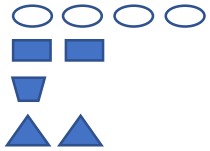
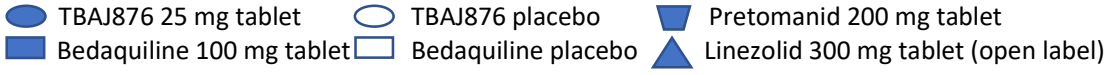
Day 1 to Week 8 *QD for 8 weeks*			**Week 9 to Week 26** *QD for 18 weeks*		
Blinding	Regimen	Number of tablets	Blinding	Regimen	Number of tablets
☐ Open label ☒ Blinded	B-Pa-L		☒ Open label ☐ Blinded	B-Pa-L	

Table 13: 2HRZE/4HR Regimen

Day 1 to Week 8 *QD for 8 weeks*			**Week 9 to Week 26** *QD for 18 weeks*		
Blinding	Regimen	Number of tablets	Blinding	Regimen	Number of tablets
☒ Open label ☐ Blinded	HRZE	Up to 5 tablets *(per weight band)*	☒ Open label ☐ Blinded	HR	Up to 5 tablets *(per weight band)*

Key and Unit dose strength/s



HRZE (isoniazid 75 mg + rifampicin 150 mg + pyrazinamide 400 mg + ethambutol 275 mg combination tablets)

HR (isoniazid 75 mg + rifampicin 150 mg combination tablets)

Instructions for Administration

All TBAJ876 and bedaquiline regimens are to be taken with a meal and with a full glass of water (approximately 240 mL) at approximately the same time each day.

HRZE/HR will be taken orally QD with a glass of water (approximately 240 mL). HRZE/HR ***should not be taken with a meal*** (generally no closer to meals than 1 hour before or 2 hours after a meal).

The daily dose of HRZE and HR will be based on the participant's weight at screening as follows:

Table 14: HRZE Weight Band

Weight Band	Weight Range (kg)	Number of Tablets
1	30-39	2
2	40-54	3
3	55-70	4
4	≥71	5

A daily supplement of Vitamin B6 will be taken with HRZE and/or HR, per each country's National TB Treatment Guideline.

Packaging

All IMP will be provided in weekly or bi-weekly participant kits as per the treatment regimens described above.

- TBAJ876-Pa-L Arms
    - Weeks 1 to 8: TBAJ876 (and/or placebo), pretomanid, and bedaquiline (and/or placebo) will be filled into a blinded weekly combination kit. Linezolid will be packaged in separate open-label kits for ease of dose reduction if needed.
    - Weeks 9 to 15: HR will be packaged in open-label bi-weekly kits
    - Weeks 16 to 26 (only for MGIT MTB positive participants at Week 8 and/or with TB symptoms at Week 15): HR will be packaged in open-label bi-weekly kits.
- B-Pa-L Arm
    - Weeks 1 to 8: Bedaquiline (and/or placebo), pretomanid, and TBAJ876 (and/or placebo) will be filled into a blinded weekly combination kit. Linezolid will be packaged in separate open-label kits for ease of dose reduction if needed.
    - Weeks 16 to 26: Bedaquiline and pretomanid will be filled into an open label weekly combination kit.
      Linezolid will be packaged in separate open-label kits for ease of dose reduction if needed.
- HRZE/HR Control Arm
    - Weeks 1 to 8: HRZE will be packaged into open-label bi-weekly kits for ease of dispensing by participant weight band.
    - Weeks 9 to 26: HR will be packaged into open-label bi-weekly kits for ease of dispensing by participant weight band.

Labeling

The packaging of each participant kit will be labeled with, at a minimum, the following information:

- Name of sponsor.
- Name of medication.
- Dosage, quantity, and method of administration.
- Reference/lot number.
- The statement “For Clinical Trial Use Only”.
- Space for completion of Name of Investigator and Site Number.
- MedID: medication identification number if applicable.
- Storage conditions.
- Period of use.
- The statement “Keep out of reach of children”.
- Expiry date.
- Directions for use.
- Local regulatory requirements.
- Space for completion of participant number and visit/date dispensed.

Please refer to the Pharmacy Manual for detailed packaging and labeling information.

Missed Doses

A missed dose of IMP can be taken within 12 hours of the regular dosing time. If more than 12 hours have passed, the participant should skip the dose and restart IMP the following day.

Doses of linezolid that are missed due to interruption of linezolid should not be made up later in the trial. See Section 9.5 for details on protocol-allowed IMP modifications.

9.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm that appropriate temperature conditions, as per details on IMP labeling, have been maintained during transit for all IMP received and stored at the site, and that any discrepancies are reported and resolved before use of the IMP.

Only participants randomised to the trial may receive IMP and only authorized site staff may supply or administer IMP. All IMP 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.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Upon completion or termination of the trial, all unused and/or partially used IMPs must either be returned to TB Alliance (or designated

vendor) who will arrange for destruction or destroyed at the site as agreed with TB Alliance after final accountability has been confirmed.

The investigator/designee will immediately inform TB Alliance of any quality issues arising with respect to the IMP. TB Alliance will take whatever action is required should such a situation arise.

Further guidance and information for the handling, storage, accountability, and final disposition of unused IMP are provided in the pharmacy manual.

9.3. Measures to Minimize Bias: Randomisation and Blinding

Participants will be randomised to one of the 5 regimens in a 1:1:1:1:1 ratio, using an IRT system which will stratify based on country and severity of disease (AFB 3+ and/or bilateral cavitation) to allocate participants evenly across the regimens by country and severity of disease burden. Information and directions will be provided to each site via the IRT user manual. TBAJ876 and bedaquiline will be blinded, while pretomanid, linezolid, and HRZE will be open label in Treatment Period 1. Treatment Period 2 is open label for all treatment regimens.

9.3.1. Blinding and Procedures for Breaking the Blind

This trial is partially blinded (Section 7.1). The blind for a participant must not be broken by the site or TB Alliance except in the case of a medical emergency, where treatment of a participant is influenced by the knowledge of what dose of TBAJ876 or bedaquiline the participant is receiving.

The investigator should discuss with TB Alliance's Medical Monitor (or designee) prior to breaking the blind unless knowledge of the treatment regimen is required urgently for a safety concern. TB Alliance's Medical Monitor should be informed of the blind break within 24 hours if not discussed prior.

The IRT will be programmed with blind-breaking instructions, described in the user manual. TB Alliance reserves the right to break the blind to fulfil any regulatory requirements regarding reporting of SAEs.

If a participant is unblinded under such circumstances, they are not required to be withdrawn from the trial.

The blind may be broken for reasons such as unblinded analyses required for interactions with regulators (Section 12.7) or DSMC review (Section 13.1.5). In the case of unblinding to support regulatory interactions or DSMC reviews, the participants and investigators will remain blinded to individual participant treatment assignments.

9.4. IMP Adherence

During the trial, the investigator will be responsible for ensuring participants are taking IMP correctly and are fully trained on how IMP is to be taken. Directly observed therapy can be implemented as per local SOC, guidelines, and practices.

The participant's IMP kit will be checked for unused tablets at each visit during the treatment periods.

A record of the quantity of IMP dispensed to and returned by each participant will be maintained and reconciled with IMP and adherence records.

9.5. Treatment Modification(s)

At no time should the participant be treated with a single agent. If any of the components other than linezolid need to be interrupted, the entire regimen must be interrupted. Dose adjustments are not allowed for TBAJ876, bedaquiline, pretomanid, or HRZE.

9.5.1. Linezolid Dose Modification

In the event of linezolid-specific toxicities, the following should be considered and implemented per guidance in Section 11.4.7:

- One-step reductions (maximum 2 steps) in the dose of linezolid.
  - 600 mg QD to 300 mg QD, 300 mg QD to 0 mg QD (temporary interruption).
- Participants who have a linezolid reduction can go back to a higher dose (1 step or 2 steps).

TB Alliance's Medical Monitor should be notified of all dose modifications.

9.5.2. Treatment Interruption or Discontinuation

Treatment Period 1

For participants experiencing suspected drug related toxicities due to drugs in the regimen other than linezolid (described above), the full regimen may be interrupted for up to 14 cumulative doses during Treatment Period 1. Participants will continue with trial visits while the IMP is interrupted. The number of missed doses will be made up by a treatment extension starting at the end of Week 8. The participant will return to the site for an EOT Make-up Period 1 visit after making up all the missed doses before proceeding to Treatment Period 2. If <4 doses were missed, the participant is required to make up those missed doses by the Week 8 visit, but there is no need to perform the EOT Make-up Period 1 visit. If the participant misses >14 cumulative doses, they will be discontinued from the trial and referred to the NTP. See Section 10.1.

Participants who become pregnant during Treatment Period 1 will be discontinued from the trial and referred to the NTP. See Section 10.1 and Section 11.4.5.

Treatment Period 2

The full regimen may be interrupted for up to 28 cumulative days during Treatment Period 2. The number of doses missed during Treatment Period 2 will be made up after Week 15 or Week 26. The participant will return to the site for an EOT Make-up Period 2 visit after making up all the missed doses, before proceeding to follow up. If <6 doses were missed, the participant is required to make up those missed doses, but there is no need to perform the EOT Make-up Period 2 visit. If a participant misses more than 28 cumulative doses during Treatment Period 2, the participant will be discontinued from the trial and referred to the local NTP. See Section 10.1.

9.5.3. Rechallenge

When IMP is interrupted due to an AE, participants may restart the IMP. Rechallenge after interruption due to an AE is only allowed once.

Refer to Section 11.4.7.1 for details on the restart/rechallenge process for IMP interruptions due to elevated liver enzymes.

9.6. Treatment of Overdose

Receiving ≥3 doses of IMP (any regimen component) within 1 day or receiving ≥2 doses in 1 day for more than 2 days in a row is considered an overdose for this trial.

In the event of an overdose, the investigator or treating physician should:

- Contact TB Alliance's Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with TB Alliance's Medical Monitor, whether the IMP should be interrupted or whether the dose should be reduced (linezolid only).
- Closely monitor the participant for any AEs/SAEs and laboratory abnormalities.
- Document the quantity and duration of the excess dose.

9.7. Concomitant Medications and Other Treatments

Concomitant medications taken 30 days prior to screening until the end of the trial (52 weeks after the EOT) should be collected in EDC and medical records.

Concomitant medications should be kept to a minimum during the treatment periods of the trial. However, if concomitant medications are necessary for the participant's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the investigator. For any concomitant medications given as a treatment for a new condition or worsening of an existing condition occurring after signing of the ICF, the condition must be documented on the Adverse Event pages of the eCRF.

The prescribing information for all concomitant medications should be consulted and reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected to prevent any potentially serious and/or life-threatening drug interactions.

For participants receiving HRZE or HR, any aluminium-containing antacids should be taken at least 1 hour after the IMP dose.

Table 15: Prohibited Concomitant Medications

Medication category or name	Period prohibited	Examples including, but not limited to
All medicinal products used to treat pulmonary TB (applicable to all treatment regimens)	At any time during the trial (screening to end of follow-up period)	gatifloxacin, moxifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole
Isoniazid prophylaxis as TPT preventative for participants living with HIV (applicable to all treatment regimens)	At any time during the trial (screening to end of follow-up period)	isoniazid*
Monoamine Oxidase Inhibitors (due to linezolid, applicable to TBAJ876-Pa-L and B-Pa-L regimens)	During treatment with IMP and 14 days before or after treatment with IMP	phenelzine, isocarboxazid, selegiline, tranylcypromine

*Isoniazid is part of the 2HRZE/4HR regimen and is permitted as a component of the regimen.

The following concomitant medications should be avoided during and for 14 days after treatment with IMP (some drugs have specified duration limitations in italics), to prevent possible drug interactions with the IMP.

Table 16: Concomitant Medications to be Avoided

Medication category or name	Examples including, but not limited to
Any drug known to be hepatotoxic (applicable for all treatment regimens)	Antibiotics: amoxicillin-clavulanate, sulfamethoxazole-trimethoprim, ciprofloxacin; NSAIDs, acetaminophen Statins, amiodarone; Valproate, phenytoin; Methotrexate
Any drug known to prolong QTc interval (applicable to TBAJ876-Pa-L and B-Pa-L regimens)	Amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin or other quinolones, and thioridazine. *Treatment with fluoroquinolones (as they are known to prolong QTc), are strongly*

Medication category or name	Examples including, but not limited to
	discouraged in the trial. They should only be used to treat intercurrent non-TB infections and if the benefit of treatment outweighs the risk of prolonged QTc.
Any drug known to induce significant myelosuppression (due to linezolid, applicable to TBAJ876-Pa-L and B-Pa-L regimens)	Chloramphenicol, phenylbutazone, quinidine, sulphadiazine, albendazole, fenbendazole, clozapine
Systemic use of strong CYP3A4 inhibitors, *for more than 14 consecutive days* (applicable to TBAJ876-Pa-L and B-Pa-L regimens)	Azole antifungals (ketoconazole, voriconazole, itraconazole, fluconazole), ketolids such as telithromycin; macrolide antibiotics other than azithromycin, grapefruit juice, ritonavir, cobicistat
Systemic use of strong and moderate CYP3A4 inducers *should be avoided 14 days before and during treatment* (applicable to TBAJ876-Pa-L and B-Pa-L regimens)	phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins[#], dexamethasone
Sensitive CYP3A4, CYP2C8, CYP2C9, CYP2C19 substrates and/or P-gp substrates. (applicable to only 2HRZE/4HR regimen)	Antifungals: ketoconazole, fluconazole, itraconazole, voriconazole Statins: fluvastatin, simvastatin, pitavastatin Class Ia antiarrhythmics: quinidine, disopyramide Cardiovascular: calcium antagonists (amlodipine, diltiazem, nifedipine, verapamil, nimodipine, nisoldipine, and isradipine), beta-blockers (bisoprolol, metoprolol, and propranolol), enalapril, imidapril, losartan, warfarin, digoxin Tricyclic antidepressants: amitriptyline and nortriptyline Antipsychotic: haloperidol, clozapine and aripiprazole Hypoglycemic agents: repaglinide, nateglinide, and sulfonylureas Sleeping medications: diazepam, benzodiazepines, buspirone, zopiclone, and zolpidem; fexofenadine, imatinib, gefitinib, and irinotecan.
Serotonergic antidepressants (TBAJ876-Pa-L and B-Pa-L regimens)	fluoxetine, paroxetine, sertraline, citalopram, escitalopram, duloxetine, venlafaxine, desvenlafaxine, levolminacipran
CYP2C8, CYP2C9, and CYP2C19 substrates (applicable to all treatment regimens)	paclitaxel, warfarin, mephenytoin

Medication category or name	Examples including, but not limited to
In vitro studies show that pretomanid is an inducer of CYP2C8 while the studies are inconclusive regarding the potential of pretomanid to induce CYP2C9 and CYP2C19. In vivo induction cannot be excluded as no clinical studies have been performed.	
OAT3 substrates, (applicable to TBAJ876-Pa-L and B-Pa-L regimens) If pretomanid is co-administered with OAT3 substrate drugs, monitor for OAT3 substrate drug-related adverse reactions and consider dosage reduction for OAT3 substrate drugs, if needed. *Refer to the prescribing information of the co-administered drug for dosage reduction information.*	methotrexate, indomethacin, ciprofloxacin
BCRP, OATP1B3, and P-gp substrates (applicable to TBAJ876-Pa-L and B-Pa-L regimens). *In vitro studies indicate that pretomanid is an inhibitor of BCRP, OATP1B3, and P-gp. No clinical studies have been performed to investigate these interactions. Therefore, it cannot be excluded that co-administration of pretomanid with sensitive OATP1B3 substrates, BCRP substrates, and P-gp substrates may increase their exposure. If substrates of OATP1B3, BCRP, or P-gp are co-administered, monitor for drug-related adverse reactions to the co-administered medicinal product.*	OATP1B3 substrates - valsartan, statins BCRP substrates - rosuvastatin, prazosin, glyburide, sulfasalazine P-gp substrates - digoxin, dabigatran, etexilate, verapamil Note: dolutegravir and tenofovir are substrates of P-gp and BCRP. They are allowed as part of an ARV regimen for HIV. Adverse reactions and blood levels will be monitored (see Section 11.5.2).
Caution should be used in treating diabetic participants receiving insulin or oral hypoglycemic agents as cases have been reported of hypoglycemic reactions when patients on these agents have been treated with linezolid. (applicable to TBAJ876-Pa-L and B-Pa-L regimens)	Insulin, glipizide, glicazide, glimepiride, metformin, rosiglitazone, pioglitazone
Strong P-gp inhibitors *for more than 3 consecutive days* (applicable to TBAJ876-Pa-L and B-Pa-L regimens).	cyclosporine, dronedarone, lapatinib, ranolazine

#Rifamycin is part of the HRZE/HR regimen and is permitted as a component of the regimen

9.7.1. Recommendations for Concomitant Use of Anti-Malarials

The following treatments for malaria are recommended for concomitant use with the IMP, should it be necessary:

- Proguanil/atovaquone, or
- Artesunate plus sulfadoxine-pyrimethamine

These recommendations are based on the potential for QT prolongation by bedaquiline and many anti-malarials. Due to the extended half-life of bedaquiline, commencing anti-malarial treatment containing drugs that could prolong the QT interval shortly after discontinuing bedaquiline is not recommended.

9.7.2. Antiretroviral Therapy

Participants living with HIV will be required to be treated with DTG, TFV, and 3TC combination at least during the treatment phase of the trial. Participants randomised to the 2HRZE/4HR regimen or receiving HR during Treatment Period 2 in the TBAJ876 arms can use any ARV compatible with the regimen. Participants who test positive for HIV at screening should initiate ARV treatment within 14 days of starting IMP.

10. EARLY DISCONTINUATION FROM TRIAL

10.1. Discontinuation from Trial

A participant will be discontinued from the trial due to the following:

- Death.
- Lost to follow-up (see Section 10.3 for definition).
- Withdrawal of consent.
- If a participant randomised to the 2HRZE/4HR (control) arm develops treatment failure or relapse.
- Reinfection.
- Withdrawal of consent.
- If a participant misses >14 doses and >28 doses during treatment periods 1 and 2, respectively. Make up of missed doses is described in Section 9.5.2.
- Due to an AE that, in the opinion of the investigator and TB Alliance, is likely to endanger the participant if dosing is continued (See Section 13.3.3 for details on follow-up procedures for AEs).
- At the specific request of TB Alliance or premature termination of the trial by TB Alliance.
- Pregnancy during Treatment Period 1 for all treatment regimens and during Treatment Period 2 for the B-Pa-L regimen (see Section 11.4.5)
- At the investigator's discretion if the participant fails to comply with the protocol, including non-adherence with the IMP.
- In the opinion of the investigator, it is in the best interest of the participant.
- Myco-discrepancies (discrepancies between the rapid test susceptibility result used to randomise participants and MGIT DST result on sputum samples collected at screening) that after the evaluation process require a change from protocol-defined treatment (refer to the Mycobacteriology Discrepancy Guideline).
- Re-treatment without documentation of active disease based on trial efficacy endpoints.

Where possible, any participant who discontinues participation in the trial before their last scheduled trial visit should complete an early discontinuation visit and be referred to the local NTP. No additional follow-up visits are required except where unscheduled visits are needed for ongoing AEs that led to discontinuation from trial and for pregnancies.

Note: Participants randomised to one of the experimental arms (TBAJ876-Pa-L and B-Pa-L arms) who relapse after completion of treatment will be retreated in the context of the current trial with 2HRZE/4HR provided that DST does not reveal resistance to any of the drug components. Participants re-treated will be followed for 26 weeks after completion of re-treatment (see Section 7.1).

In the case of treatment failure or relapse in participants randomised to the control arm (2HRZE/4HR), the participant will be referred to the local NTP for further management, and treating physicians will be provided with the DST results and medical report from the investigator (see Section 7.1).

10.2. Participant Withdrawal of Consent

A participant may withdraw from the trial at any time at their own request (withdrawal of consent). The participant may request or not destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

Should a participant withdraw consent due to an AE, the specific AE must be reported as the reason for withdrawal of consent.

10.3. Lost to Follow-up

Should a participant not be reachable to attend trial visits, the following should be conducted and documented in the site trial records before confirming a participant is lost to follow-up:

- Three documented telephone contact attempts (participant and/or relative).
- Letter to be sent to the participant's physical address via courier, or a similar process (adapted per country specific requirements/circumstances).

If no feedback is received within 30 days of courier confirmation of letter delivery to and receipt by the participant, then the participant may be considered lost to follow-up.

11. TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the Trial Flow Chart (Section 3.2). Prospective approval of protocol waivers or exemptions will not be granted by TB Alliance.

Urgent safety concerns should be discussed with TB Alliance's Medical Monitor immediately upon occurrence or awareness.

Adherence to the trial design requirements, including those specified in the Trial Flow Chart, is essential and required for trial conduct.

11.1. Visit Schedule

11.1.1. Screening

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 will record reasons for screening failure, as applicable.

Screening assessments should be initiated as soon as possible for a potential participant and can occur on different days within 11 days prior to randomisation on Day 1. Screening assessments may be repeated once during the 11-day screening period. A participant who fails screening will not be re-screened.

11.1.2. Unscheduled Visits

Any visit which is conducted in addition to those required by the Trial Flow Chart (Section 3.2) should be considered unscheduled regardless of the reason for the visit. The assessments which are undertaken as part of an Unscheduled Visit should be as clinically indicated.

The following situation(s) require an Unscheduled Visit(s):

- For any medical reason, as determined by the investigator or participant.
- As required, if after having converted to culture negative, the participant has an MTB confirmed positive culture at or after the last visit of Treatment Period 2 (Week 15 or Week 26). The participant should return for unscheduled visit(s) to provide additional sputum samples, at a minimum of 7 days apart, or to document that the participant is not able to produce a sputum sample.
- Determination of the participant's outcome status required sputum culture results at the following time points during the trial:
    - Follow-up Week 26 and Follow-up Week 52.
    - Early Discontinuation, if applicable.

    Note, at least one of the following criteria should be met at these time points to confirm a participant's outcome status:

    - Two sequential negative sputum culture results; or
    - Two sequential MTB positive sputum culture results; or

- Has been unable to produce sputum after documentation of 2 negative sputum cultures with no intervening MTB positive and the participants is clinically asymptomatic.

If the participant does not fall into one of the above categories, the site should continue to collect sputum samples x 2 (2 spot samples at least 30 minutes apart, under the coaching and observation of the trial staff) at a minimum of 7 days apart until the participant falls into one of the above categories.

11.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the Trial Flow Chart.

Definitions of bacteriologic treatment failure, relapse, and reinfection are provided in Table 17.

Table 17: Definitions of Treatment Failure, Relapse, and Reinfection

	Definition
Treatment Failure	**TREATMENT FAILURE DIAGNOSED bythe end of treatment IF ≥2 of A, B, or C are satisfied; OR if D is satisfied** **A. Clinical Disease Persistence** Persistent TB symptoms or signs without an alternative explanation. **B. Chest X-ray Progression** Abnormalities that are compatible with active TB disease (cavitation, infiltrates, consolidation) with clear evidence of no improvement or progression compared with start of treatment without an alternative, more likely explanation. C. Unconfirmed positive MGIT putum sample result after having achieved culture negative status (defined as 2 negative culture results at least 7 days apart) . **D. Confirmed MTB positive sputum culture** Failure to attain culture negative status by the end of treatment or failure to maintain culture negative status (defined as 2 positive culture results at least 7 days apart after achieving culture negative status).
Relapse or Reinfection	**RELAPSE or RE-INFECTION DIAGNOSED during follow up** in participants with culture negative status by the EOT, **IF ≥2 of A, B, or C are satisfied; OR if D is satisfied** **A. Clinical Disease Progression** New or recurrent TB symptoms or signs after complete resolution at the EOT without an alternative, more likely explanation.

	B. Chest X-ray Progression Abnormalities that are compatible with active TB disease (cavitation, infiltrates, consolidation) with clear evidence of progression compared with the EOT without an alternative, more likely explanation. **C. Microbiological Evidence of Recurrence** Sputum sample taken after the EOT is smear positive OR GeneXpert positive (if >26 weeks after EOT); OR unconfirmed MGIT MTB positive culture;. **D. Confirmed MTB Positive Sputum Culture** Sputum culture MTB positive on 2 consecutive samples, at least 7 days apart,.

Whole genome sequencing analysis will be utilized to determine if the participant is experiencing a relapse or a re-infection.

Whole genome sequencing will establish the number of SNPs/variants to determine if the strains can be considered identical (relapse) or different (re-infection), using the following cut offs that have been determined from previously published reports (REMoxTB and RIFAQUIN trials)

- ≤12 SNPs different = Relapse
- ≥100 SNPs different = Reinfection
- >12 and <100 SNPs different = Indeterminate

Indeterminate results will be reviewed and adjudicated on case-by-case basis and are likely to be rare.

Additional sequence analysis may be performed and/or additional samples may need to be tested.

Any additional investigations will be documented on the 'WGS Indeterminate Proforma' which will also include a final conclusion of 'relapse' or reinfection' based on these further reviews.

A participant will be considered a relapse unless there is sufficient evidence to support a classification of re-infection.

11.2.1. Mycobacteriology Assessments

Mycobacteriology procedures are listed here. All mycobacteriology procedures are described in a separate document, the Mycobacteriology Laboratory Manual.

11.2.1.1. Sputum-based Assessments

Ideally, 2 sputum samples are collected at each visit at the research site under the coaching and observation of the trial staff (spot samples). Every effort is to be made to collect

sputum samples. However, the inability to produce sputum under experienced staff coaching is considered equivalent to having a negative culture (favourable) result.

At Screening (Days -11 to -1), the following tests will be performed on one of the sputum samples:

- Smear microscopy for AFB
- Rapid molecular tests for isoniazid resistance
- GeneXpert MTB/RIF Ultra
- Liquid Culture (MGIT) followed by an identification test to detect MTB and obtain the TTP
- Lipoarabinomannan concentration determination (LAM assay), if available

In case it is technically not possible to obtain an appropriate result(s) for any test listed above with the first sample, these tests will be repeated on the second sample or on a freshly collected spot sputum.

The following analyses will be performed on all sputum samples and every visit:

- Smear microscopy for AFB
- MGIT culture followed by an identification test to detect MTB and obtain the TTP

Using the MGIT culture results, the following derived variables will be assessed for evaluation of the efficacy endpoints:

- Bacteriologic treatment failure/relapse/re-infection
- Time to sputum culture conversion to negative status
- Number of participants with sputum culture conversion to negative status
- Sputum culture TTP curves through 8 weeks of treatment

At Day 1 and Weeks 4, 8, 15, and 26 besides smear microscopy and MGIT culture, the additional tests will be performed on both samples:

- GeneXpert MTB/RIF Ultra
- LAM assay, if available

11.2.1.2. Mycobacterial Characterization

Additional mycobacterial characterization tests (susceptibility testing for rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide, TBAJ876, bedaquiline, linezolid, and pretomanid; and WGS) will be performed on MTB-positive, non-contaminated cultures from the following visit periods:

- First positive between Screening through Week 4 (only randomised participants)
- Week 8, Week 15, and Week 26 for participants not responding to therapy (i.e., who have not converted to culture negative by those time points)
- First MTB-positive culture during post-treatment follow-up in participants who have converted to negative culture.

- Discontinuation of treatment at/after Week 8
- Additional visits as required by the TB Alliance mycobacteriology team

When phenotypic DST and WGS results on Day 1 samples become available, any results that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be reviewed by the trial medical and mycobacteriology team, in consultation with the investigator, to determine whether that participant is unlikely to respond to IMP and should therefore be discontinued from the trial and referred to the NTP. If by the time this information is available, the participant has already converted to sputum negative culture, they will be offered the option to continue the assigned treatment and remain in the trial. As such, participants with myco-discordant results may be allowed to remain in the trial. Participants with phenotypic DST and WGS results on Day 1 samples that are discordant with the screening molecular test results used to qualify a participant's eligibility for the trial will be classified as a late exclusion and will be described separately. See the Mycobacteriology Discrepancy Guideline for additional details.

11.2.1.3. Storage of Mycobacterial Samples

MTB isolates from all MTB-positive, non-contaminated cultures, as well as the extracted MTB DNA from the applicable isolates, will be stored at validated laboratories for potential further work.

11.2.2. TB Symptoms Profile

The TB Symptoms Profile (found in the Subject Questionnaires Guideline) will record participants' ratings of the severity of common TB symptoms.

11.3. Safety and Tolerability Assessments

Planned time points for all safety assessments are provided in the Trial Flow Chart, except for the timing and obtaining of ECGs and PK samples, which are described in more detail in this section.

11.3.1. Physical Examinations

A full physical examination will include, at a minimum, height (at screening) and weight measurements and assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

Additional physical examinations will be directed by any symptoms described by the participant, but a cardiovascular examination must be performed at all visits.

11.3.2. Vital Signs

Systolic and diastolic blood pressure (mmHg) are to be measured supine (after 5 minutes of rest) using an appropriately sized cuff and using the same type of sphygmomanometer by the same observer, if possible, at each relevant visit.

- Respiratory rate will be recorded as breaths per minute.
- Heart rate will be recorded as beats per minute.

- Temperature will be measured using a digital temperature scanner.

11.3.3. Electrocardiograms

Central ECG analysis will be performed. Central reading of screening results will be used to determine eligibility.

The investigator's assessment will still be required at all visits in which an ECG is performed and should be recorded as normal or abnormal.

The central cardiologist's assessment will be communicated to the site after centralized reading and will include the following measures: heart rate, PR interval, RR interval, QT, QTc, QTcF, and QRS.

Methodology:

- Timing and registration technique for ECGs will be standardized for all participants and will be described in a separate document which will be provided prior to the trial start.
- Participants should be supine for at least 5 minutes prior to each 12-lead ECG evaluation.
- ECGs are to be recorded for 10 seconds.
- All ECGs are to be performed in triplicate except at the Screening Visit, which is a single ECG.
- ECGs should be done before any venipuncture and sputum collection when both are included in a visit.

Table 18: Order of ECG and PK Sample Collection

Day 1	Day 15	Week 8 and EOT Make-up Period 1	Week 12	Week 26 and EOT Make-up Period 2	Early Trial Discontinuation Visit
1) pre-dose ECG	1) pre-dose ECG	1) pre-dose ECG	1) pre-dose ECG	1) pre-dose ECG	1) ECG
2) pre-dose PK sample	2) pre-dose PK sample	2) pre-dose PK sample	2) pre-dose PK sample	2) pre-dose PK sample	2) PK sample
3) Administer IMP	3)Administer IMP	3) Administer IMP	3) Administer IMP	3) Administer IMP	
	4) 3-hour PK	4) 3-hour PK			
	5) 5-hour ECG	5) 5-hour ECG			
	6) 5-hour PK sample	6) 5-hour PK sample			

Note: Accurately record the timing of both the ECG and the blood sample. Only participants who receive TBAJ876-Pa-L or B-Pa-L will have trial drug PK samples taken.

11.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 (Section 13.2) for the list of clinical laboratory tests to be performed; see the Trial Flow Chart (Section 3.2) for the timing and frequency.

The investigator must review the laboratory report for each visit, document this review, and record any clinically significant changes occurring during the trial as an AE.

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 safety laboratory tests with abnormal values considered clinically significant during participation in the trial should be repeated and evaluated as clinically indicated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or TB Alliance's Medical Monitor.

The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start.

11.3.5. Pregnancy Testing

Urine pregnancy testing will be performed for women of childbearing potential only, whether they are sexually active or not.

11.3.6. Serology: HIV, CD4 Count, Viral Load

If a participant's HIV status is unknown at the time of screening, an HIV test will be performed. If an HIV test was performed within 1 month prior to trial start, it should not be repeated as long as documentation of results can be provided (ELISA and/or Western Blot and/or Electro-Chemiluminescence). Where required by regulatory authorities or ECs, a separate consent for this test to be performed will be obtained from participants during the written informed consent process.

Prior to HIV testing and on receipt of the results, participants will be counselled on HIV by trained site staff or counsellors.

For all known participants living with HIV, viral load and CD4 are required at screening.

11.3.7. Chest X-ray

Chest x-rays (digital image) will be obtained and read locally by the investigator or designee. Digital images will be provided to TB Alliance; this process will be described in a separate document, the Radiology Manual. Chest X-rays should be taken as per trial flow chart (Section 3.2) but can be performed at any time during the study as clinically indicated. The investigator is responsible for the review and interpretation of the chest x-ray for the participant's randomisation into the trial.

11.3.8. Visual Acuity

This examination can be performed by any trained trial staff. Methodology and requirements will be detailed in the Ophthalmology Guideline for the following assessments.

- Ophthalmology History (screening only);
- Visual Acuity Test or Distance Vision.

If a participant has corrected vision, the visual acuity test should be conducted in the same manner (with or without glasses/contacts) for that participant throughout the trial.

11.3.9. Medical History

In addition to recording medical history, prior medications, treatments, and smoking history will also be recorded.

11.3.10. Quality of Life Assessment

The quality of life questionnaire will be completed at the time points described in the Trial Flow Chart. Quality of life data will be collected using the WHOQOL-BREF (found in the Subject Questionnaires Guideline).

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

The definitions of AEs, SAEs, and unsolicited and solicited AEs can be found in Appendix 3 (Section 13.3). Treatment-emergent AEs are defined as any AE that occurs after the first dose of IMP and within 28 days after the last dose of IMP.

AEs 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 (see Section 10).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

All AEs and SAEs will be collected from the signing of the ICF until the Follow-up Week 52 visit (end of trial).

Medical occurrences that begin after obtaining informed consent will be recorded as AEs. If an AE started before signing of the informed consent, but is ongoing at trial start, it should be recorded as medical history. If the pre-existing medical occurrence worsens during the trial, an AE will be recorded.

All SAEs will be recorded and reported to TB Alliance or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to TB Alliance within 24 hours of the investigator's awareness.

Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the trial, and they consider the event to be reasonably related to the IMP or trial participation, the investigator must promptly notify TB Alliance.

11.4.2. Method of Detecting AEs and SAEs

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

11.4.3. 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 AEs will be followed until satisfactory clinical resolution or stabilization; or the end of the Follow-up Period or Early Trial Discontinuation Visit; and all queries on these AEs have been resolved or the participant is lost to follow-up (as defined in Section 10.3). Further information on follow-up procedures is provided in Appendix 3 (Section 13.3.3).

11.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to TB Alliance of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the IMP under clinical investigation are met.

TB Alliance has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. TB Alliance will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC, 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 TB Alliance will review and will notify the IRB/EC, if appropriate according to local requirements.

11.4.5. Pregnancy

All women of childbearing potential will be instructed to contact the investigator immediately if they suspect they might be pregnant (for example, missed or late menses) during participation in the trial. The investigator will immediately notify TB Alliance of any pregnancy that is discovered during IMP administration. Pregnancy forms will be completed for all pregnancies reported during the clinical trial, as defined below. In addition, the investigator will report to TB Alliance follow-up information regarding the outcome of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for 6 months.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to TB Alliance within 24 hours of learning of the female participant's pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post-trial pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the TB Alliance as described in Section 11.4.4.

If pregnancy is suspected while the participant is receiving IMP (except participants who are receiving HR during Treatment Period 2), the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the participant will be discontinued from the trial, and the participant will be referred to the NTP. Participants receiving HR who become pregnant during Treatment Period 2 may continue to take IMP.

11.4.6. Disease-related Events and/or Disease-related Outcomes not Qualifying as AEs or SAEs

Symptoms of the disease under evaluation (pulmonary TB) experienced by the participant while on the trial will be assessed by the investigator. If the symptom has worsened while the participant is in the trial, and the investigator assesses it as clinically significant, it will be recorded as an AE.

If there is no change, and the investigator assesses the symptom as due to the participant's condition, it will not be recorded as an AE, and this will be noted in the participant's source documentation.

All TB-related symptoms that meet SAE criteria will be recorded and reported as a SAE.

11.4.7. Monitoring for Specific Toxicities – AESIs

Monitoring for specific toxicities is based upon target organs as defined in nonclinical toxicity studies outlined in the Investigator's Brochures and package inserts.

Adverse events still ongoing at the EOT in the trial will be followed until satisfactory clinical resolution or stabilization or until the end of the follow-up period and until all queries on these AEs have been resolved. Grade 3 and Grade 4 laboratory abnormalities and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization. Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In these cases, follow-up will be the responsibility of the treating physician. If there is uncertainty, the investigator can discuss appropriate follow-up with TB Alliance's Medical Monitor.

Note: For all Grade 3 or Grade 4 laboratory toxicities, participants should have a confirmatory measurement within 48 hours where possible. The recommendations for managing participants below assume the laboratory abnormalities of concern have been confirmed.

11.4.7.1. ALT, AST, ALP, and Bilirubin Elevations

Note: The text below is a guideline. Ultimately, it is the investigator's responsibility to manage the participant appropriately.

TB Alliance reviewed all relevant data on liver safety across the pretomanid program. With the B-Pa-L regimen, the magnitude of ALT and/or AST elevation was rarely above 8 x ULN and was usually not accompanied by symptoms or bilirubin elevation. Participants who interrupted treatment due to LFT elevation and were rechallenged afterwards with the B-Pa-L regimen, were all able to complete the treatment with no reoccurrence of the LFT elevation.

Based on the above information, as well as the label information for pretomanid and bedaquiline, TB Alliance's safety monitoring and safety management guideline in clinical trials with bedaquiline (or its analog), pretomanid, and an oxazolidinone regimen is as follows:

During the informed consent process, it is important that participants are made aware of the risk of liver dysfunction in the trial, the symptoms that may be associated with liver injury, and also how serious this can be if ignored. Participants should be explicitly made

aware of the need to seek medical attention/contact the site if they become unwell while in the trial. There should be specific reference made to the signs and symptoms associated with hepatotoxicity at every visit (especially gastrointestinal upset) and reinforce the need to seek medical attention should these occur. Recommend avoidance of alcohol and other hepatotoxic medications including herbal supplements (please refer to the concomitant medications [Section 9.7]).

Monitor symptoms and signs (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly) and laboratory tests (ALT, AST, ALP, and bilirubin) at Day 1 and weekly while on treatment in the first month, then every other week during the second month, then monthly, and as needed (per protocol schedule).

If an increase in transaminases is observed, please follow the guidance specified below:

<u>If ALT/AST >3 x to ≤5 x ULN:</u>

Complete evaluation to identify the cause for increase in ALT/AST:

- Discontinue other potentially hepatotoxic medications.
- Counsel participant to avoid alcohol and other hepatotoxic medications including herbal supplements (ensure adherence to concomitant medications guidance in the protocol).
- Monitor ALT, AST, ALP, GGT, and bilirubin at least weekly until return of values to baseline levels or <2 x ULN.
- Monitor for signs and symptoms (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly).
- Evaluate for alternative etiologies, including testing for viral hepatitis (such as HBV, HCV, HAV, and can be extended to CMV and EBV).

<u>If ALT/AST >5 x ULN</u> (requires confirmation as soon as possible):

- Interrupt all trial medication **immediately**.
- Evaluate and monitor participant as per instructions for ALT >3 x to ≤5 x ULN (see above).
- Trial drug may be re-introduced when levels return to <2 x ULN or baseline values (if baseline levels were ≥2 x ULN) or if an alternative explanation is identified; weekly monitoring should continue to ensure that the re-introduction of trial medication is not associated with a new ALT/AST increase.
- Per the investigator's discretion, permanently discontinue trial medication if ALT values increase again after re-introduction (confirmation is not required).
- Maximum interruption allowed is 14 days and 28 days for Treatment Period 1 and 2, respectively, after which the permanent discontinuation of the trial medication is required.

Stop trial treatment, discontinue from the trial, and refer the participant to the NTP if:

- Aminotransferase elevations are accompanied by total bilirubin elevation >2 x ULN.

- Aminotransferase elevations are >5 x ULN and persist beyond 2 weeks.
- Aminotransferase elevations are >10 x ULN (confirmed within 48 hours).

Re-challenge is not allowed in these circumstances (unless an alternative explanation was identified that was responsible for the above observations, and it is deemed safe to re-challenge given the removal of the other risk factors, as allowed by the protocol).

11.4.7.2. Monitoring Bedaquiline and TBAJ876 Toxicities

11.4.7.2.1. Lipase

Contact TB Alliance's Medical Monitor to review any lipase elevation of Grade 3 (≥3.0 to <5.0 x ULN) or Grade 4 (≥5.0 x ULN). For participants with confirmed Grade 3 or Grade 4 elevations of lipase, the investigator should consider pausing the full regimen, pending further evaluation.

11.4.7.2.2. Musculoskeletal System and Cardiac Muscle

Myalgia

Participants with Grade 2 signs and symptoms should be followed closely. Participants with Grade 3 or Grade 4 signs and symptoms should be discussed with TB Alliance's Medical Monitor to consider pausing the IMP regimen, pending further evaluation which includes measurement of CPK levels.

- Grade 2 (muscle pain causing greater than minimal interference with usual social and functional activities)
- Grade 3 (muscle pain causing inability to perform usual social and functional activities)
- Grade 4 (disabling muscle pain causing inability to perform basic self-care functions)

CPK

For participants with elevations in CPK of potential clinical concern (Grade 2 increase or higher), the investigator should check the CPK-MB subunit (plus cardiac troponin I and myoglobin if positive) and ask the participant about any recent strenuous physical activity. If the CPK-MB subunit and/or troponin I and/or myoglobin is abnormal, the investigator must pause the regimen and discuss with TB Alliance's Medical Monitor.

11.4.7.2.3. Cardiac Rhythm Disturbances

Participants with cardiac rhythm disturbances that are Grade 3 (non-life-threatening symptoms AND non-urgent intervention indicated) or Grade 4 (life-threatening arrhythmia OR urgent intervention indicated) should have IMP paused immediately and be monitored closely. The investigator should inform TB Alliance's Medical Monitor of any Grade 3 or Grade 4 cardiac rhythm disturbances immediately to jointly determine further action.

QTc prolongation

If the QTcF is ≥500 msec, the ECG should be repeated, and serum electrolytes should be evaluated. If the second ECG also has a QTcF of ≥500 msec, the full regimen should be

paused, and TB Alliance's Medical Monitor should be informed immediately to jointly determine further action.

New left bundle branch block or Mobitz type 2 or complete heart block

Recordings with artifacts that interfere with the interpretation of the ECG should be repeated to confirm the findings. If the automatic reading report from the ECG machine indicates a new left bundle branch block or Mobitz type 2 or complete heart block, the result is to be checked and confirmed by the investigator. If this is confirmed by the investigator, dosing is to be paused immediately until the reading has been confirmed by the central cardiologist; the participant is to be treated per the investigator's clinical judgment and the Medical Monitor should be notified. If it is confirmed by the central cardiologist, the participant is to stop trial treatment, be discontinued from the trial, and referred to the NTP.

11.4.7.3. Monitoring Linezolid Toxicities

The following are guidelines for decisions to pause, reduce, and to resume linezolid in response to the onset and resolution of known linezolid-specific toxicities. These are guidelines, and decisions must be made in the context of the entire clinical status of the participant. The Medical Monitor should be contacted to discuss the management of the participant.

11.4.7.3.1. Neurological

Participants who receive linezolid with co-administration of a serotonergic agent, including anti-depressants, should be monitored closely for signs of serotonin syndrome (see Section 9.7). The investigator should determine whether the full regimen or the concomitant agent should be discontinued for those who experience signs or symptoms of serotonin syndrome, such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.

Linezolid and/or the full regimen should be paused for participants experiencing a seizure. TB Alliance's Medical Monitor should be contacted to review details and discuss the management of the participant.

11.4.7.3.2. Myelosuppression

The haematologic parameters of haemoglobin and counts of neutrophils and platelets are variable from measurement to measurement. While decreases in any of these may be caused by linezolid toxicity, decreases of concern should be evaluated in the context of the participant's full clinical status and alternate explanations. The guidelines below are for situations of concern when it is considered likely that linezolid has caused the decrease. For information about linezolid dose modifications see Section 9.5.1.

Anaemia

Consider dose modification/interruption of linezolid, at the investigator's discretion, if haemoglobin falls below 9 g/dL or 90 g/L (Grade 3) and significantly below baseline, or if hemoglobin falls >25% of baseline. Further management of the participant should be discussed with the Medical Monitor.

Leukopenia

Consider dose modification/interruption of linezolid, at the investigator's discretion, if the absolute neutrophil count falls below 600/mm^3 or 0.60 x 10^9/L (Grade 3) and significantly below baseline. Ideally confirm with a repeat test before making further decisions, as absolute neutrophil counts can have diurnal and other variability. Further management of the participant should be discussed with the Medical Monitor.

Thrombocytopenia

Consider dose modification/interruption of linezolid, at the investigator's discretion, if platelets fall below 50,000/mm^3 or 50 x 10^9/L (Grade 3) and significantly below baseline. Ideally confirm with a repeat test before making further decisions. Further management of the participant should be discussed with the Medical Monitor.

11.4.7.3.3. Peripheral Neuropathy

The decision to reduce the dose, or to pause linezolid until symptoms improve, is a judgment based on changes in signs and symptoms identified by the investigator and informed by discussion with the trial participant. As general guidance, consider pausing and/or reducing linezolid when the grade of a neuropathy sign or symptom increases by a grade to Grade 2 or greater. If it is clear that linezolid caused the neuropathy, consider resuming linezolid at half the dose when the neuropathy improves.

11.4.7.3.4. Optic Neuropathy

A participant with visual symptoms of concern or change in visual acuity of 2 lines or more should be referred to an ophthalmologist for evaluation with a retinal examination. Any changes as assessed by the ophthalmologist that raise concern that an optic neuropathy may be developing should be discussed with the Medical Monitor and linezolid should be paused. If a likely or definite optic neuropathy is confirmed, linezolid should be permanently discontinued.

11.4.7.3.5. Lactic Acidosis

Lactic acidosis as a toxicity of linezolid should be considered if a participant develops signs and symptoms suggestive of lactic acidosis, e.g., new onset of nausea and vomiting, extreme tiredness, trouble breathing or rapid shallow breaths, that are not otherwise explained. Such participants should have lactate measured and, as indicated, a full evaluation including pH and bicarbonate. Note that lactate should not be measured in participants who have no symptoms of concern, as elevated asymptomatic lactate may be common, and it is difficult to interpret the clinical relevance of this. Also evaluate whether any concomitant medications, such as ARV therapies, may be associated with lactic acidosis and consider pausing them at the same time linezolid is interrupted (or in a staggered manner) until the acidosis resolves.

11.5. Pharmacokinetics

11.5.1. Trial Drugs (TBAJ876, Bedaquiline, Pretomanid, Linezolid)

11.5.1.1. General Procedures

Whole blood samples of approximately 4 mL will be collected from all participants except those in the HRZE regimen for measurement of plasma concentrations of TBAJ876, bedaquiline, pretomanid, linezolid, and their metabolites.

- Pre-dose samples will be collected on days specified in the Trial Flow Chart (Section 3.2).
- In addition, on Day 15 and at Week 8, additional samples will be collected.
    - On Day 15, participants who are *not* in the intensive PK sub-group (see Section 11.5.1.2) will have samples collected pre-dose and 1, 3, and 5 hours post-dose.
    - At Week 8, all participants will have samples collected pre-dose and 1, 3, and 5 hours post-dose.

It is important that on each visit day when PK sampling is done the participant's IMP administration for that day be done at the site after the pre-dose sample and, on Day 15 and at Week 8, before the post-dose samples. Investigational medicinal product in all regimens other than the HRZE regimen should always be taken with a meal; therefore, when IMP is administered on site on days when PK samples are drawn, participants need to be provided with a meal. Additionally, when IMP is taken at the trial site, participants will be checked for IMP administration by the investigators or trial personnel via the hand-and-mouth procedure.

On each visit day when PK sampling is done, the site should ask the participant for and record the dates and times of the 2 previous IMP administrations.

Sites may bring a participant back at the subsequent scheduled visit or at an unscheduled visit prior to the following scheduled visit to collect PK samples to ensure the blood draws are done in accordance with protocol requirements (for example if the participant already took the medication on a day when a pre-dose sample is to be obtained). The site should make every effort to collect all 3 post-dose samples on Day 15 and at Week 8 when operationally and logistically feasible.

If the full regimen is paused, PK sampling should be delayed until the full regimen is resumed. PK sampling should be completed even if the participant's linezolid dose has been lowered or linezolid alone has been paused or permanently discontinued.

Instructions for the collection and handling of biological samples will be provided by TB Alliance. The actual date and time (24-hour clock time) of each sample will be recorded. In addition, the dates and times of the 2 doses of IMP taken prior to every pre-dose PK sample will be collected in the eCRF.

11.5.1.2. Additional Procedures for Intensive PK Sub-group

Participants at some sites will be asked to engage in an intensive PK sub-group to collect a larger number of PK samples spread across the 24 hours after the dose on Day 15. Participants who consent will be hospitalized for at least Day 15 and will have samples collected pre-dose and 3, 4, 5, 8, 12, 16, 20, and 24 hours post-dose on Day 15.

11.5.2. ARV Drugs (Tenofovir [TFV] and Dolutegravir [DTG])

Whole blood samples of approximately 4 mL will be collected from all participants living with HIV, for measurement of plasma concentrations of TFV and DTG. Pre-dose samples will be collected on days specified in the Trial Flow Chart (Section 3.2). It is important that on each visit day when PK sampling is drawn the participant's ARV administration for that day be done at the site after the pre-dose sample. On each visit day when PK sampling is done, the site should ask the participant for and record the date and time of the previous administration of TFV and DTG. Sites may bring a participant back at the subsequent scheduled visit or at an unscheduled visit prior to the following scheduled visit to collect PK samples to ensure the blood draw is done in accordance with protocol requirements (for example if the participant already took the medication on a day when a pre-dose sample is to be obtained).

Instructions for the collection and handling of biological samples will be provided by TB Alliance. The actual date and time (24-hour clock time) of each sample will be recorded. In addition, the dates and times of the administration of TFV and DTG taken prior to every pre-dose PK sample will be collected in the eCRF.

Tenofovir (TFV) and DTG are P-gp substrates, and TBAJ876 has been found to increase $AUC_{0\text{-last}}$ and C_{max} of the sensitive P-gp substrate digoxin by 53% and 18%, respectively, in a clinical drug interaction trial (see Section 5.2.1). Also, pretomanid may be an inhibitor of P-gp, based on in vitro results, although a clinical drug interaction trial has not been conducted. Samples will be used to evaluate the PK of TFV and DTG. Measured PK levels may also be used to help interpret AEs that are suspected of relationship with TFV or DTG.

11.6. Exploratory Sample Collection

Exploratory research will be limited to MTB-related tests, and/or PK or PD related tests for all trial drugs and their metabolites. Interactions between trial drugs and their metabolites and concomitant medications may also be explored.

All trial participants will be asked to consent to the following:

- The storage of all unused blood, sputum, and urine samples (as available) for long-term storage, for the purpose of possible additional exploratory research after the end of the trial.
- Additional blood and urine samples for exploratory research will be collected at Day 1, Weeks 4, 8, 15, and 26.

If a participant does not agree to have their unused and/or additional samples stored, they can still participate in this trial. Unused samples for which consent was not obtained will not be used and will be destroyed upon completion of the trial.

All samples for which consent had been obtained will be stored for up to 10 years after completion of the trial (or according to local regulations), and the analysis process will not be linked to any personal identifiers. Analysis of these samples is not intended for diagnostic or prognostic purposes, and results will not be communicated back to the investigators or participants. The research may begin at any time during the trial or following completion of the trial during the post-trial storage period.

11.7. Pandemics, Epidemics, and Other Disease Outbreaks

All trial activity will be conducted in accordance with relevant local, regional, and national guidances around pandemics (e.g. COVID-19), epidemics, or other disease outbreaks. In order to minimize health risks to trial participants and site personnel, additional assessments and/or procedures (which may include but are not limited to, symptom assessments and diagnostic tests) may be implemented at the discretion of the investigator and TB Alliance's Medical Monitor, beyond those required for this protocol.

12. STATISTICAL ANALYSIS

The SAP, which will contain details of the analyses specified in this section, will be written and signed off prior to randomisation of the first participant.

12.1. Analysis Population

12.1.1. Intent-to-treat (ITT) Population

The ITT population will include all randomised participants who took at least 1 dose of trial drug.

12.1.2. Modified Intent-to-treat (MITT) Population

The primary analysis population will be the MITT population defined as participants who are randomised and take at least 1 dose of trial drug, without late exclusions, which are defined as:

- Lack of MTB culture positive on Day 1. Screening culture can be used to determine inclusion in MITT population if Day 1 sputum culture is contaminated or unavailable or,
- Discrepancies between screening rapid test result and corresponding culture or WGS result revealing DR-TB.

The MITT will be the primary population for all efficacy analyses. For the other secondary endpoints i.e., Follow-up Week 26 and 52, 2 MITT analyses will be performed:

- Where all unassessable participants are excluded from the analysis (main analysis).
- Where all unassessable participants are considered unfavourable.

Unassessable participants are defined in the SAP.

12.1.3. Per Protocol Population

The PP population is the MITT population excluding participants with major protocol deviations. For the primary endpoint, the PP population will also exclude participants who received less than 7 weeks of the regimen, referred to as PP 7 weeks. For all secondary endpoints, the PP population will exclude participants who received less than 80% of trial medication, referred to as PP80.

Full details of all the analysis populations will be defined in the SAP.

12.2. Sample Size Determination

Sample size for this trial will be at least 60 participants per treatment regimen. Sample size assumptions below are selected to be conservative to achieve adequate power given minimal dropout prior to Week 8.

Based on data from previous trials of DS-TB, it is assumed that the probability of participants achieving stable sputum culture conversion to negative status by Week 8 of Treatment Period 1 in the control regimen (HRZE) is 0.50 (Gillespie et al, 2014; Dorman et al, 2021). The number of events and power required is based on comparison of the primary endpoint,

time to stable sputum culture conversion to negative status using data from weekly cultures through Week 8 of Treatment Period 1.

The trial will require approximately 76 events (stable sputum culture conversion to negative status) among approximately 120 randomised participants. This number ensures that a 2-sided, $\alpha = 0.05$ logrank test procedure will have 80% power when the true hazard ratio of TBAJ876 vs. HRZE is 2.0 and 90% power when the hazard ratio is 2.2 (Table 19). It is assumed that calculations are sufficiently conservative to ensure that the required number of events will be observed by the time the analysis is conducted using Week 8 data. In order to minimize Type I error, the comparisons for inference will be ordered starting with the highest TBAJ876 dose regimen.

Table 19: Sample Size Calculation

Number per regimen	80% power		90% power	
	% culture converted in 876 regimen by 8 weeks	Hazard ratio	% culture converted in 876 regimen by 8 weeks	Hazard ratio
60	75%	2.0	78%	2.2

This sample size is considered adequate to characterize the tolerability profile of TBAJ876. The probability of observing at least 2 events is 80% for an event that has a true incidence of 5% (Table 20).

Table 20: Probability (%) of Observing X or More AEs by True Frequency (N = 60)

Number of AEs observable in trial	True frequency of AE (%)			
	1/20 (5%)	1/10 (10%)	3/20 (15%)	1/5 (20%)
1 or more	95%	99%	>99%	>99%
2 or more	80%	95%	>99%	>99%
3 or more	58%	95%	>99%	>99%
4 or more	35%	86%	99%	>99%

12.3. Primary and Secondary Endpoint Analysis

The MITT population will be the primary population for all efficacy analyses.

12.3.1. Primary Analysis

The primary endpoint is time to stable sputum culture conversion to negative status over 8 weeks using data from weekly cultures up to and including Week 8 in the TBAJ876 regimens. Stable sputum culture conversion to negative status is defined as 2 negative results (at least 7 days apart without an intervening MTB positive). If the first negative result occurs at Week 8, the Week 9 culture result can be used for the confirmatory negative result.

The primary hypothesis is that for participants randomised to a TBAJ876-containing regimen (at least 1 TBAJ876 regimen), the time to culture negativity by 8 weeks will be superior, compared to the participants who are treated with the standard HRZE regimen.

The primary efficacy analysis uses a time to event approach to compare culture conversion to negative status between the investigational regimens and control regimen based on the

MITT population. Participants not completing 8 weeks will be censored at their last visit date. A stratified logrank test will be used to compare time to stable sputum culture conversion to negative status between the 2 regimens with the stratification factors country and severity of disease (AFB 3+ and/or bilateral cavitation). Estimates of the hazard ratios will be calculated using a stratified Cox proportional hazards model with treatment group as the sole covariate and the stratification factors country and severity of disease. Corresponding 2-sided 95% CIs will also be presented.

Time to stable sputum culture conversion to negative status will also be summarized using the Kaplan-Meier method and displayed graphically. Median event times (and other quartiles) and 2-sided 95% CI for each time will be provided.

A multivariate Cox proportional hazards model will be used to explore predictors (e.g. baseline characteristics) associated with time to stable sputum culture conversion to negative status. The hazard ratio associated with each of the baseline covariates will be presented along with associated 95% CIs.

A sensitivity analysis pooling all TBAJ876 regimens will also be conducted.

Details regarding additional sensitivity analyses of the primary endpoint will be detailed in the SAP.

Analysis of the primary endpoint will be repeated for the PP (7 weeks) population. Subgroup analyses, such as by country and disease severity, will be performed.

The primary analysis will be conducted when all participants reach Week 8 of the trial (see Section 12.7 for further details).

12.3.2. Secondary Analyses

12.3.2.1. Key Secondary Analyses

The proportion of participants with a favorable outcome at 26 weeks after EOT based on the MITT population for B-Pa-L vs. 2HRZE/4HR.

For this analysis, participants will be classified as having a favourable, unfavourable, or unassessable outcome at 26 weeks after EOT, as applicable. Favourable outcome is defined as participants who maintain culture negative status through to 26 weeks after EOT without re-treatment for TB. The definition for unassessable will be further detailed in the SAP.

Two MITT analysis will be performed:

- Where all unassessables are unfavourable.
- Where all unassessables are excluded from the analysis.

In this case, the analysis where all unassessables are excluded from the analysis will be the main analysis.

The number and proportion of participants with a favourable outcome and corresponding 95% CIs will be summarized for the 3 doses of TBAJ876 arms and B-Pa-L.

A stratified analysis of the risk difference adjusting for country and severity of disease using Cochran-Mantel-Haenszel weights will be used to compare B-Pa-L with 2HRZE/4HR.

Stratum-adjusted risk differences and corresponding 95% CIs will be provided for B-Pa-L vs. 2HRZE/4HR.

Logistic regression modelling will also be used to explore predictors of achieving a favourable outcome (e.g. baseline characteristics).

Further analyses will explore the relationship between the primary endpoint, time to stable sputum culture over 8 weeks, and whether or not a participant achieves a favourable outcome. For example, Kaplan-Meier estimates and graphs for time to stable sputum culture will be generated separately for participants who achieve a favourable outcome and participants who do not achieve a favourable outcome. In addition, the Cox proportional hazards model for time to stable sputum culture will be extended to include a covariate for participants achieving a favourable outcome (yes/no).

The number of unassessables will also be displayed. Time to favourable outcome may also be displayed graphically using a Kaplan-Meier graph.

Additional analyses will also be conducted to explore predictors of a favourable outcome (e.g. baseline characteristics).

12.3.2.2. Other Secondary Analyses

12.3.2.2.1. Proportion of Participants who Meet the Criteria to Stop Treatment at Week 15

The proportion of participants who meet the criteria to stop treatment at Week 15 will be summarized based on the MITT population. This endpoint is of interest for the 3 doses of TBAJ876 arms.

Inability to produce sputum will be considered as a negative MGIT culture result. If Week 8 MGIT culture results are inconclusive (i.e., contamination of sputum sample), the culture sample obtained at Week 9 can be used to determine whether a participant met the criteria. If a participant has a negative MGIT culture result but discontinues prior to Week 15, the participant will be classified as having met the criteria to stop treatment as long as there are no TB symptoms (participants with symptoms that have an alternative explanation are eligible to complete treatment at Week 15) prior to discontinuation. If MGIT result is MTB positive and/or there are still TB symptom(s), participants will be classified as not meeting the criteria for stopping treatment.

Analyses of the proportion of participants who meet the criteria to stop treatment at Week 15 will be similar to that of the key secondary endpoint in Section 12.3.2.1.

In addition, a dose response analysis (e.g. Cochran-Armitage test for trend) will be conducted to evaluate the relationship between increasing dose of TBAJ876 (25 mg, 50 mg, 100 mg) and the effect of TBAJ876 in terms of proportion of participants meeting the criteria to stop treatment at Week 15.

12.3.2.2.2. Proportion of participants with a favourable outcome at 26 weeks and 52 weeks after the EOT

The proportion of participants with a favourable outcome at 26 week and 52 weeks after EOT will be analyzed for the 3 dose levels of TBAJ876 relative to 2HRZE/4HR similar as described for B-Pa-L vs. 2HRZE/4HR in Section 12.3.2.1.

In addition, the proportion of participants with a favourable outcome at 52 weeks after EOT will be analyzed for B-Pa-L vs. 2HRZE/4HR as described in Section 12.3.2.1.

12.3.2.2.3. Relapse Rates

Relapse rates at 26 weeks after EOT, and separately at 52 weeks after EOT (end of follow-up period) based on the MITT population will be summarized as described for favourable outcome. Participants with relapse are classified based on the definition in Table 17.

12.3.2.2.4. Impact of Treatment Duration on Favourable Outcome and Relapse Rates (26 Weeks and 52 Weeks after EOT)

To support the main analyses of favourable outcome and relapse rates performed based on the randomised treatment arms and further explore the impact of treatment duration on efficacy, analyses will be performed for 2 subgroups for each experimental treatment arm:

(1) participants meeting the criteria to stop treatment at Week 15, and

(2) participants not meeting the criteria to stop treatment (continuing treatment to Week 26).

In an exploratory fashion, analyses will be conducted to descriptively compare these subgroups within each TBAJ876-Pa-L arm to examine whether treatment duration impacts effect of TBAJ876 for a particular dose, as well as to compare these subgroups between the TBAJ876 dose arms to examine whether the impact of treatment duration varies by TBA876 dose.

The resulting subgroups by arm and treatment are below:

- TBAJ876 25 mg-Pa-L, met the criteria to stop treatment at Week 15
- TBAJ876 25 mg-Pa-L, did not meet the criteria to stop treatment at Week 15
- TBAJ876 50 mg-Pa-L, met the criteria to stop treatment at Week 15
- TBAJ876 50 mg-Pa-L, did not meet the criteria to stop treatment at Week 15
- TBAJ876 100 mg-Pa-L, met the criteria to stop treatment at Week 15
- TBAJ876 100 mg -Pa-L did not meet the criteria to stop treatment at Week 15

Analysis of favourable outcome as described in Section 12.3.2.1 will be performed within each of the aforementioned subgroups. Similarly, analysis of relapse rates as described in Section 12.3.2.2.3 will be performed by subgroup. The results of these subgroup analyses will also be displayed graphically.

Logistic regression modelling will be used to further explore the relationship between favourable outcome and early completion of treatment, and separately relapse rates and early completion of treatment.

12.3.2.2.5. Bactericidal Activity

To assess the bactericidal activity over 2 weeks of TBAJ876 or bedaquiline in combination with pretomanid and linezolid, relative to HRZE, in adult participants with newly diagnosed, smear-positive, pulmonary DS-TB, BA_{TTP}(1-15) as determined by the rate of change in TTP over Days 1 to 15 of treatment, represented by the model-fitted log(TTP) as calculated by

the regression of the observed log(TTP) counts over time. A similar analysis will be performed to assess bactericidal activity over 8 weeks (BA_{TTP}(1-56)).

12.3.2.2.6. Other Analyses

Time to stable sputum culture conversion to negative status over 8 weeks comparing B-Pa-L vs. HRZE will be analyzed as described in Section 12.3.1 for the primary analysis.

To evaluate stable sputum culture conversion to negative status over time of TBAJ876 or B-Pa-L relative to 2HRZE/4HR during the treatment period, the proportion of participants with stable sputum culture conversion to negative status will be presented for each treatment regimen at Weeks 4, 6, 8, 12, 15, 20, and 26.

Time to stable sputum culture conversion to negative status through 8 weeks of treatment will also be analyzed by severity group (low, high) and separately by country.

Efficacy endpoints assessed at Week 8, with the exception of time to stable sputum culture conversion to negative status, will also be analyzed using data when all participants have received 8 weeks of IMP after any missed doses have been made up at the end of Treatment Period 1.

12.3.2.3. Exploratory Analyses

Change from baseline in measurements of biomarker assays (potentially LAM and other assays), through the course of treatment and the post-treatment follow-up period relative to treatment outcome will be evaluated. Additional analyses will be conducted to correlate response measured with MGIT at Day 1 and Weeks 4, 8, 15, and 26 with AFB smear and exploratory biomarkers. Correlation analyses will also be performed to look at the relationship of MGIT culture results at Weeks 2, 4, and 8 with favourable outcome at 26 weeks and 52 weeks after the EOT.

Logistic regression modelling will be used to explore predictors (i.e., baseline characteristics) of MGIT negative culture (yes/no) at Week 8 of treatment.

12.3.3. Multiplicity Considerations

Statistical testing for the primary endpoint will be performed using the Hochberg method to control the overall Type I error rate at 5% for the following comparisons: TBAJ876 high dose vs. HRZE, TBAJ876 medium dose vs. HRZE, and TBAJ876 low dose vs. HRZE.

No attempt will be made to adjust for multiplicity when testing secondary and exploratory endpoints. All secondary and exploratory endpoints subjected to significance testing will be assessed at an unadjusted 2-sided level of significance of 0.050.

12.4. Safety Analyses

The primary safety evaluation will be performed at Week 8 to align with the time point of interest for the primary efficacy endpoint. Details regarding the conduct of this analysis will be included in the SAP. Safety will also be assessed using all data available on-trial.

Key safety endpoints will also be analyzed separately by subgroups defined by whether or not a participant met the criteria to stop treatment at Week 15 in order to explore whether the additional duration of treatment impacted the overall safety and tolerability of the 3

doses of TBAJ876-Pa-L or B-Pa-L. Summaries will be presented for each subgroup in Section 12.3.2.2.4 overall on-trial as well as over time with particular focus on Weeks 15 to 26 and beyond. Key safety endpoints include, but are not limited to, incidence of TEAEs (including by severity, drug relatedness, seriousness, leading to early discontinuation), post-Day 1 QT/QTc intervals and changes from Day 1, and incidence of laboratory abnormalities.

The incidence of all-cause mortality will be summarized for each treatment group.

All AEs will be coded using MedDRA and will be presented by preferred term within each MedDRA system organ class.

Treatment-emergent AEs are defined as AEs which started at or after the first administration of IMP and includes those events started prior to the first administration of IMP but which worsened after the first intake. Adverse events starting after the last administration of IMP and within 28 days after the last dose of IMP will be regarded as treatment emergent.

The incidence of the following events will be summarized for further medical analysis:

- Incidence of TEAEs
- Incidence of TEAEs by severity
- Incidence of TEAEs by DAIDS toxicity grade
- Incidence of drug-related TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to discontinuation
- Incidence of TEAEs leading to death.

Cardiovascular Safety: QT intervals will be adjusted using Fridericia's correction. QT/QTc values and changes from pre-dose (average of Screening and Day 1 values) at each time point will be summarized using descriptive statistics by time of collection. These will be presented as descriptive analyses, and no inferential tests will be carried out.

Post-Day 1 QT/QTc intervals will be classified into the following categories:

- QT/QTc <450 msec
- 450 msec <QT/QTc <480 msec
- 480 msec <QT/QTc <500 msec
- QT/QTc >500 msec

QTc changes from Day 1 will be classified into the following categories:

- increase <30 msec,
- 30 msec and <60 msec, and
- increase >60 msec.

Frequency counts will be used to summarize the number of participants at each time point according to the above categories.

Electrocardiogram results will be also classified as normal or abnormal (investigator assessment) and summarized using frequency counts by time of collection.

Visual acuity: Descriptive statistics, including changes from Day 1, will be summarized and listed by participant for visual acuity assessments. Categorical data for changes in visual acuity from Day 1 will be summarized in a frequency table for the right and left eye, respectively.

Descriptive statistics of **neuropathy** data derived from Brief Peripheral Neuropathy Screen. Categorical data for observed signs and symptoms of neuropathy will be summarized in frequency tables, including changes in signs and symptoms from Day 1.

Other safety variables: laboratory parameters, physical examination, vital signs (see Appendix 3, Section 13.3), and concomitant medications. Descriptive summary statistics will be presented. For laboratory parameters, values and changes from Day 1 over time as well as shifts from Day 1 will be summarized. The incidence of liver-related laboratory abnormalities will be explored. Select parameters may also be plotted over time.

12.5. Pharmacokinetics

For each analyte and each scheduled sampling time, the plasma concentration will be summarized by descriptive statistics including the mean, SD, CV, median, minimum, maximum, geometric mean, and geometric CV (%).

12.6. Pharmacokinetics/Pharmacodynamics

Plasma concentrations will be summarized in tables and figures. Concentrations from intensively sampled profiles and, as feasible, from sparse sampling will be used to compute summary metrics of exposure such as C_{max} and AUC over a dosing interval for TBAJ876 and its M3 metabolite, bedaquiline and its M2 metabolite, pretomanid, and linezolid.

Relationships may be explored between drug exposure and efficacy and safety endpoints, including concentration vs. QTc. If so, planning details and results will be included in a separate modeling plan and report.

12.6.1. Pharmacogenetics

For study participants not randomised to 2HRZE/4HR who sign a separate informed consent, a blood sample will be drawn at Day 1 (or at other time point during the trial if not obtained at Day 1) for possible exploratory pharmacogenetic testing. An individual who is unwilling to consent to such a procedure may still participate in the trial. The sample may be used to identify genes that contribute to PK variability of TBAJ876 and bedaquiline, i.e., variability in blood levels of those drugs and their metabolites, such as (but not necessarily restricted to) genes for drug-metabolizing enzymes or drug-transport proteins. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-trial assessment of genetic factors involved in the PK of TBAJ876 and bedaquiline or other drugs of the diarylquinoline class. The pharmacogenetic analyses may begin at any time during the trial or following completion of the trial, and results of pharmacogenetic analyses may not be reported with the trial summary.

12.7. Interim Analyses

There will be 1 planned unblinded interim analysis which will contain results by treatment group in aggregate and will include the primary analysis. This will occur after all participants have completed 8 weeks of treatment.

Additional analyses may be performed during trial conduct to support organizational decision making or interactions with regulatory authorities. In this circumstance, a limited number of individuals will have access to individual treatment assignments. The sites, participants, and individuals involved in the day-to-day trial conduct will remain blinded to individual treatment information, until the end of the trial.

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1. Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

13.1.1. Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

13.1.2. Financial Disclosure

If the trial is conducted under a USA IND, investigators and sub-investigators will provide TB Alliance with sufficient, accurate financial information as requested to allow TB Alliance 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 trial and for 1 year after completion of the trial.

13.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the participant or their legally authorized representative and answer all questions regarding the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, data privacy requirements (where applicable), and the IRB/EC or trial center before any trial specific procedures, including withdrawal from current treatment, are completed.

The medical record must include a statement that written informed consent was obtained before the participant was screened for the trial 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 trial.

A copy of the signed ICF(s) must be provided to the participant.

13.1.4. Data Protection

Participants will be assigned a unique identifier by TB Alliance. Any participant records or datasets that are transferred to TB Alliance 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 trial-related data will be used by TB Alliance 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 TB Alliance, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

13.1.5. Data Safety Monitoring Committee (DSMC)

A DSMC will be appointed for the trial. The primary responsibility of the DSMC will be to act in an advisory capacity to TB Alliance to safeguard the interests of trial participants by monitoring participant safety, assessing participant risk vs. benefit, and assessing data quality and general evaluation of the trial progress. Its activities will be delineated in a DSMC charter that will define the membership, responsibilities, and the scope and frequency of data reviews. The DSMC will operate on a conflict-free basis independently of TB Alliance and the trial team. It will comprise at least 3 voting members that include at least 2 clinicians and 1 statistician. The DSMC may have an organizational meeting prior to commencement of the trial. The DSMC will have meetings where it will review unblinded data during a closed session. These meetings will be planned at regular intervals (at least every 6 months and ad-hoc). TB Alliance or the DSMC may convene ad hoc meetings based on rates of SAEs and/or to review results of interim analyses or if safety concerns arise during the trial. After its assessment, the DSMC will recommend to TB Alliance continuation, modification, or termination of the clinical trial.

13.1.6. Dissemination of Clinical Trial Data

See Section 13.1.10 for information about the dissemination of clinical trial data.

13.1.7. Data Quality Assurance

All participant data relating to the trial will be recorded on printed or electronic CRFs unless it is transmitted to TB Alliance 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 eCRFs will be provided in the eCRF Completion Guidelines.

The investigator must permit trial-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (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.

TB Alliance or designee is responsible for the data management of this trial including quality checking of the data in the trial database.

TB Alliance assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for not less than 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP, 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 TB Alliance. No records may be transferred to another location or party without written notification to TB Alliance.

13.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are retained at the investigator's site.

Direct data capture may be used for source data. Data 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 trial. Current medical records must be available.

Source documents are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents will include, but are not limited to, progress notes, in-patient hospital records, electronic data, screening logs, and recorded data from automated instruments.

As defined in the monitoring plan, trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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 trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

13.1.9. Trial Termination and Site Closure

TB Alliance may suspend enrolment into the trial, suspend treatment of ongoing participants, or terminate the trial to ensure that participants' safety and welfare are protected. The entire trial, or individual sites, may be terminated for any of the following reasons:

- changes in scientific knowledge that lead to a negative impact on the risk/benefit profile for participants.
- request of TB Alliance or competent health authorities, IRB, or EC.
- if recruitment cannot be completed in the specified time frame.
- if the permit to manufacture or import IMP is revoked.

- if the IMP becomes commercially available or another mechanism is available to provide the IMP to the participant.

TB Alliance reserves the right to discontinue the trial prior to inclusion of the intended number of participants but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating participants immediately after notification. As directed by TB Alliance, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

An individual trial center that is determined to be unsuitable by TB Alliance, competent health authorities, or EC may be terminated, without affecting the other trial sites.

Except for those situations outlined in Section 10.2, no other formal stopping rules for individual participants, parts of the trial, or the entire trial, will be defined.

13.1.10. Publication Policy

The definition of publication for this purpose is any public presentation of the data emerging from this trial.

All unpublished information given to the investigator by TB Alliance shall not be published or disclosed to a third party, other than to the responsible IRB/EC, within the understanding of the confidentiality of their nature, without the prior written consent of TB Alliance.

Results of this research will be submitted for publication as soon as feasible upon completion of the trial in the form of a joint publication(s) between TB Alliance and investigator(s), including site clinical and laboratory investigators, as appropriate. Publication and authorship will be in accord with the International Association of Journal Editors.

Because the trial is funded, in whole or in part, by the Bill and Melinda Gates Foundation (the "Foundation"), all peer-reviewed published research relating to the trial must comply with the Foundation's Open Access Policy as described from time to time at http://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy. Specifically, (a) all peer-reviewed published research relating to the trial must be submitted for publication by TB Alliance through the Chronos Open Access Publishing Service established by the Foundation to ensure the immediate and unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the Foundation without any embargo period, and (b) all data underlying the peer-reviewed published research results must be immediately made accessible and open to the public in accordance with the Foundation's Open Access Policy. The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to TB Alliance before submission. This allows TB Alliance to protect proprietary information and to provide comments.

TB Alliance will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, TB Alliance will generally support publication of multicenter trials 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.

13.1.11. TB Alliance, Financial Aspects, Insurance, and Indemnity

The trial sponsor is TB Alliance. TB Alliance is a not for profit, product development partnership accelerating the discovery and development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with ARV therapies for those HIV-TB participants currently on such therapies and improve treatment of latent infection.

TB Alliance works with public and private partners worldwide. It is committed to ensuring that approved new regimens are affordable, adopted, and available to those who need them.

TB Alliance operates with funding mainly from the United States Agency for International Development (USAID), Bill & Melinda Gates Foundation, the Netherlands Ministry of Foreign Affairs (DGIS), and the United Kingdom Department for International Development (DFID).

The participants will not receive any incentives for their involvement in the trial. TB Alliance has made provision to reimburse the participants for out-of-pocket expenses such as travelling to and from the trial site and other miscellaneous costs as a result of their trial participation.

TB Alliance certifies that it has liability insurance coverage for itself and will provide an associated certificate upon request. The insurance does not relieve the investigators of the obligation to maintain their own liability insurance as required by applicable law. TB Alliance does not assume any obligation for the medical treatment of other injuries and illnesses.

13.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 21 will be performed by a central laboratory.

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

Table 21: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count	Hematocrit
	Red blood cell count	Myoglobin (as required)
	Haemoglobin	White blood cell count with differential
Clinical Chemistry	Albumin	Glucose
	ALT	HbA1c (screening only)
	Amylase	Lipase
	AST	Magnesium
	Alkaline phosphatase	Phosphate
	Bicarbonate/CO_2	Potassium
	Calcium (corrected for albumin)	Serum urea
	Chloride	Sodium
	Creatine phosphokinase (CPK) and CPK-MB (as required)	Thyroid Stimulating Hormone (TSH)
	Creatinine	Troponin I (as required)
	Direct, indirect, and total bilirubin	Uric acid
Urinalysis	Bilirubin	Nitrate
	Blood	pH
	Creatinine	Protein
	Glucose	Sodium
	Ketones	Specific gravity
	Leukocytes	Urobilinogen
	Micro-albumin	
	Microscopic examination (if blood or protein is abnormal)	
Pregnancy Testing	Urine pregnancy test for women of childbearing potential only, whether they are sexually active or not	
Other Screening Tests	Serology (HIV antibody, HBsAg, HAV IgM, and Anti-Hep C Ab)	
	CD4 count and viral load (for participants living with HIV)	
	Urine drug screen (cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, and barbiturates)	

Investigators must document their review of each laboratory safety report. All events of ALT or AST 3 × ULN and total bilirubin 2 × ULN (>35% direct bilirubin), which may indicate severe liver injury (possible Hy's Law), must be reported to TB Alliance in an expedited manner.

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

13.3.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical trial participant, temporally associated with the use of trial treatment, whether or not considered related to the trial treatment. 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 IMP.

Definition of Unsolicited and Solicited AE
An unsolicited AE is an AE that was not solicited using a Participant Diary and that is communicated by a participant who has signed the ICF. Unsolicited AEs include serious and non-serious AEs. Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of concern to the participant. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. Unsolicited AEs that are not medically attended nor perceived as a concern by a participant will be collected during interview with the participant and by review of available medical records at the next visit. Solicited AEs are predefined systemic events for which the participant is specifically questioned.

Events Meeting the AE Definition:
Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from Day 1, 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 conditions detected or diagnosed after IMP administration even though it may have been present before the start of the trial. Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP 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.

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE. "Lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition:

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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 trial that do not worsen.

13.3.2. Definition of SAE

An SAE is defined as any AE that, at any dose:

Results in death

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.

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 AEs. 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 Day 1 is not considered an AE.

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, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

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.

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.

13.3.3. Recording and Follow-up of AE and/or 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 reports, 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 TB Alliance or designee in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by IRBs or regulatory authorities. 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 IRBs or regulatory authorities.

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 trial and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE.

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.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.

The investigator will also consult the IB and/or PI (for marketed products) in their assessment.

For each AE/SAE, the investigator **must** document in the medical notes that they have 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 TB Alliance or designee. 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 TB Alliance or designee.

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 AEs and SAEs

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- The end of the Follow-up Period or Early Trial Discontinuation Visit (see Section 11.4.3); and
- All queries on these AEs have been resolved.

Follow-up of AEs leading to early discontinuation of IMP should be completed by the investigator via unscheduled visits or by reviewing participant medical records (see Section 11.1.2).

If a participant dies during participation in the trial, the investigator will provide TB Alliance with any available post-mortem findings.

13.3.4. Reporting of SAEs

SAE Reporting to TB Alliance or Designee
The primary mechanism for reporting an SAE to TB Alliance or designee 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 trial is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a trial participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to TB Alliance or designee by telephone.

13.4. Appendix 4: The IUATLD Scale

The IUATLD scale proposes 5 groups for reporting the results of reading smears for AFB. They should be recorded as follows:

FINDING	RECORDING
No AFB found in at least 100 fields	negative
1 to 9 AFB per 100 fields	exact figure/100/scanty positive
10 to 99 AFB per 100 fields	+
1 to 10 AFB per field in at least 50 fields	++
More than 10 AFB per field in at least 20 fields	+++

Reference: The Public Health Service National Tuberculosis Reference Laboratory and the National Laboratory Network. Minimum Requirements, Role and Operation in a Low-Income Country. International Union Against Tuberculosis and Lung Disease 1998.

13.5. Appendix 5: WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection

- Asymptomatic
- Acute retroviral syndrome

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical Stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrheic dermatitis
- Fungal nail infections

Clinical Stage 3

- Unexplained severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for >1 month
- Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant)
- Persistent oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary TB (current)
- Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained anaemia (hemoglobin <8 g/dL)
- Neutropenia (neutrophils <500 cells/µL)
- Chronic thrombocytopenia (platelets <50,000 cells/µL)

Clinical Stage 4

- HIV wasting syndrome
- Pneumocystis pneumonia

- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site)
- Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
- Extrapulmonary TB
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Cryptococcosis, extrapulmonary (including meningitis)
- Disseminated non-TB mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Candida of the trachea, bronchi, or lungs
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)
- Recurrent nontyphoidal Salmonella bacteremia
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

REF: World Health Organization. WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children; 2007

13.6. Appendix 6: Division of AIDS Toxicity Tables

Source: U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. (July 2017).

Abbreviations Utilized in the Tables

ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
BMD	bone mineral density
CNS	central nervous system
ECG	electrocardiogram
INR	international normalized ratio
IV	intravenous
LLN	lower limit of normal
NA	not applicable
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cells
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamate pyruvate transaminase
ULN	upper limit of normal

Estimating Severity Grade

For abnormalities NOT found elsewhere in the Toxicity Tables, use the scale below to estimate grade of severity:

Grade	Severity Rating	Definition
Grade 1	Mild	Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
Grade 2	Moderate	Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
Grade 3	Severe	Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
Grade 4	Potentially Life-threatening	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

General Considerations

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

For parameters not included in the following Toxicity Tables, sites should refer to the "Estimating Severity Grade" located above.

Criteria are generally grouped by body system. Criteria are for adults ≥18 years of age.

Cardiovascular				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Arrhythmia (by ECG or physical exam)	No symptoms AND no intervention indicated	No symptoms AND non-urgent intervention indicated	Non-life-threatening symptoms AND non-urgent intervention indicated	Life-threatening arrhythmia OR urgent intervention indicated
Blood Pressure Abnormalities Hypertension	140 to <160 mmHg systolic OR 90 to <100 mmHg diastolic	≥160 to <180 mmHg systolic OR ≥100 to <110 mmHg diastolic	≥180 mmHg systolic OR ≥110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR hospitalization indicated
Blood Pressure Abnormalities Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

Cardiovascular				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Ischemia or Infarction *(Report only one)*	NA	NA	New symptoms with ischemia (stable angina) OR new testing consistent with ischemia	Unstable angina OR acute myocardial infarction
Heart Failure	No symptoms AND laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR intervention indicated (e.g., oxygen)	Life-threatening consequences OR urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage *(with significant acute blood loss)*	NA	Symptoms AND no transfusion indicated	Symptoms AND transfusion of ≤2 units packed RBCs indicated	Life-threatening hypotension OR transfusion of >2 units packed RBCs indicated
Prolonged PR Interval or AV Block *(Report only one)*	PR interval 0.21 to <0.25 seconds	PR interval ≥0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR ventricular pause ≥3.0 seconds	Complete AV block
Prolonged QTc Interval (based on Bazett's formula)	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds OR ≥0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)

Cardiovascular				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Thrombosis or Embolism *(Report only one)*	NA	Symptoms AND no intervention indicated	Symptoms AND intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

Dermatologic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia *(scalp only)*	Detectable by trial participant, caregiver, or physician AND causing no or minimal interference with usual social and functional activities	Obvious on visual inspection AND causing greater than minimal interference with usual social and functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	N**A**	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyper-pigmentation	Slight or localized causing no or minimal interference with usual social and functional activities	Marked or generalized causing greater than minimal interference with usual social and functional activities	NA	NA
Hypo-pigmentation	Slight or localized	Marked or generalized	NA	NA

Dermatologic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	causing no or minimal interference with usual social and functional activities	causing greater than minimal interference with usual social and functional activities		
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus *(without skin lesions)*	Itching causing no or minimal interference with usual social and functional activities	Itching causing greater than minimal interference with usual social and functional activities	Itching causing inability to perform usual social and functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR target lesions	Diffuse rash AND vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR toxic epidermal necrolysis

Endocrine and Metabolic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Diabetes Mellitus	Controlled without medication	Controlled with medication OR modification of current	Uncontrolled despite treatment modification OR	Life-threatening consequences (e.g., ketoacidosis,

Endocrine and Metabolic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
		medication regime	hospitalization for immediate glucose control indicated	hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by trial participant, caregiver, or physician AND causing no or minimal interference with usual social and functional activities	Obvious on visual inspection AND causing pain with greater than minimal interference with usual social and functional activities	Disfiguring changes AND symptoms requiring intervention or causing inability to perform usual social and functional activities	NA
Hyperthyroidism	No symptoms AND abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities OR thyroid suppression therapy indicated	Symptoms causing inability to perform usual social and functional activities OR uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities OR thyroid replacement therapy indicated	Symptoms causing inability to perform usual social and functional activities OR uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)

Endocrine and Metabolic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Lipoatrophy (characterized by fat loss in the face, extremities, and buttocks)	Detectable by trial participant, caregiver, or physician AND causing no or minimal interference with usual social and functional activities	Obvious on visual inspection AND causing greater than minimal interference with usual social and functional activities	Disfiguring changes	NA
Lipohypertrophy (characterized by abnormal fat accumulation on the back of neck, breasts, and abdomen)	Detectable by trial participant, caregiver, or physician AND causing no or minimal interference with usual social and functional activities	Obvious on visual inspection AND causing greater than minimal interference with usual social and functional activities	Disfiguring changes	NA

Gastrointestinal				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND intervention indicated (e.g., diuretics,	Symptoms recur or persist despite intervention	Life-threatening consequences

Gastrointestinal				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
		therapeutic paracentesis)		
Bloating or Distension *(Report only one)*	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	NA
Cholecystitis	NA	Symptoms AND medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia *(Report only one and specify location)*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g.,

Gastrointestinal				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
				hypotensive shock)
Mucositis or Stomatitis *(Report only one and specify location)*	Mucosal erythema	Patchy pseudo-membranes or ulcerations	Confluent pseudo-membranes or ulcerations OR mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR tissue necrosis OR diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent AND no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR rehydration indicated (e.g., IV fluids	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation *(colon or rectum)*	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social and functional activities OR medical	Symptoms causing inability to perform usual social and functional activities OR operative intervention indicated	Life-threatening consequences (e.g., perforation)

Gastrointestinal				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
		intervention indicated		
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND no or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia	Joint pain causing no or minimal interference with usual social and functional activities	Joint pain causing greater than minimal interference with usual social and functional activities	Joint pain causing inability to perform usual social and functional activities	Disabling joint pain causing inability to perform basic self-care function
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social and functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social and functional activities	Stiffness or joint swelling causing inability to perform usual social and functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia *(generalized)*	Muscle pain causing no or minimal interference with usual social and	Muscle pain causing greater than minimal interference with usual social and	Muscle pain causing inability to perform usual social and functional activities	Disabling muscle pain causing inability to perform basic self-care functions

Musculoskeletal				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	functional activities	functional activities		
Osteonecrosis	NA	No symptoms but with radiographic findings AND no operative intervention indicated	Bone pain with radiographic findings OR operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia	BMD t-score -2.5 to -1 (if ≥30 years of age) BMD z-score -2 to -1 (if <30 years of age)	NA	NA	NA
Osteoporosis	NA	BMD t-score <-2.5 (if ≥30 years of age) BMD z-score <-2 (if <30 years of age)	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status *(for Dementia, see Cognitive, Behavioral, or*	Changes causing no or minimal interference with usual	Mild lethargy or somnolence causing greater than minimal	Confusion, memory impairment, lethargy, or somnolence	Delirium OR obtundation OR coma

Neurologic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Attentional Disturbance below)	social and functional activities	interference with usual social and functional activities	causing inability to perform usual social and functional activities	
Ataxia	Symptoms causing no or minimal interference with usual social and functional activities OR no symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance *(includes dementia and attention deficit disorder) Specify type, if applicable*	Disability causing no or minimal interference with usual social and functional activities OR specialized resources not indicated	Disability causing greater than minimal interference with usual social and functional activities OR specialized resources on part-time basis indicated	Disability causing inability to perform usual social and functional activities OR specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR institutionalization indicated
Headache	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions OR hospitalization indicated OR headache with significant impairment of alertness or other neurologic function

Neurologic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Neuromuscular Weakness *(includes myopathy and neuropathy) Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social and functional activities OR no symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social and functional activities	Muscle weakness causing inability to perform usual social and functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation
Neurosensory Alteration *(includes paresthesia and painful neuropathy) Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social and functional activities OR no symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures (new onset)	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR difficult to control (e.g., refractory epilepsy)
Seizures (pre-existing)	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR difficult to control (e.g., refractory epilepsy)

Neurologic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Stillbirth *(report using mother's participant ID) Report only one*	NA	NA	Fetal death occurring at ≥20 weeks gestation	NA
Preterm Birth *(report using mother's participant ID)*	Live birth at 34 to <37 weeks gestational age	Live birth at 28 to <34 weeks gestational age	Live birth at 24 to <28 weeks gestational age	Live birth at <24 weeks gestational age
Spontaneous Abortion or Miscarriage *(report using mother's participant ID) Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

Psychiatric				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social and functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social and functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social and functional activities requiring	NA

Psychiatric				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
			intervention or hospitalization	
Psychiatric Disorders *(includes anxiety, depression, mania, and psychosis) Specify disorder*	Symptoms with intervention not indicated OR behavior causing no or minimal interference with usual social and functional activities	Symptoms with intervention indicated OR behavior causing greater than minimal interference with usual social and functional activities	Symptoms with hospitalization indicated OR behavior causing inability to perform usual social and functional activities	Threatens harm to self or others OR acute psychosis OR behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND no wish to kill oneself	Preoccupied with thoughts of death AND wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR hospitalization indicated	Suicide attempted

Respiratory				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70 to <80% OR mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to <70% OR symptoms with intervention indicated OR symptoms causing greater than minimal interference with usual social and functional activities	Forced expiratory volume in 1 second or peak flow 25 to <50% OR symptoms causing inability to perform usual social and functional activities	Forced expiratory volume in 1 second or peak flow <25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory	Dyspnea on exertion with	Dyspnea on exertion causing	Dyspnea at rest causing inability to	Respiratory failure with

Respiratory				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Distress *Report only one*	no or minimal interference with usual social and functional activities OR wheezing OR minimal increase in respiratory rate for age	greater than minimal interference with usual social and functional activities OR nasal flaring OR intercostal retractions OR pulse oximetry 90 to <95%	perform usual social and functional activities OR pulse oximetry <90%	ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hearing Loss	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
Tinnitus	Symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated	Symptoms causing inability to perform usual social and functional activities	NA
Uveitis	No symptoms AND detectable on examination	Anterior uveitis with symptoms OR medical intervention indicated	Posterior or pan-uveitis OR operative intervention indicated	Disabling visual loss in affected eye(s)

Sensory				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Vertigo	Vertigo causing no or minimal interference with usual social and functional activities	Vertigo causing greater than minimal interference with usual social and functional activities	Vertigo causing inability to perform usual social and functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes *(assessed from Day 1)*	Visual changes causing no or minimal interference with usual social and functional activities	Visual changes causing greater than minimal interference with usual social and functional activities	Visual changes causing inability to perform usual social and functional activities	Disabling visual loss in affected eye(s)

Systemic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR mild angioedema with no intervention indicated	Generalized urticaria OR angioedema with intervention indicated OR symptoms of mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	NA
Cytokine Release Syndrome	Mild signs and symptoms AND therapy (i.e., antibody infusion)	Therapy (i.e., antibody infusion) interruption indicated AND	Prolonged severe signs and symptoms OR recurrence of symptoms	Life-threatening consequences (e.g., requiring pressor or

Systemic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	interruption not indicated	responds promptly to symptomatic treatment OR prophylactic medications indicated for ≤24 hours	following initial improvement	ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever *(non-axillary temperatures only)*	38.0 to <38.6°C or 100.4 to <101.5°F	≥38.6 to <39.3°C or ≥101.5 to <102.7°F	≥39.3 to <40.0°C or ≥102.7 to <104.0°F	≥40.0°C or ≥104.0°F
Pain *(not associated with trial agent injections and not specified elsewhere) Specify location*	Pain causing no or minimal interference with usual social and functional activities	Pain causing greater than minimal interference with usual social and functional activities	Pain causing inability to perform usual social and functional activities	Disabling pain causing inability to perform basic self-care functions OR hospitalization indicated
Serum Sickness	Mild signs and symptoms	Moderate signs and symptoms AND intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support
Unintentional Weight Loss *(excludes postpartum weight loss)*	NA	5 to <9% loss in body weight from Day 1	≥9 to <20% loss in body weight from Day 1	≥20% loss in body weight from Day 1 OR aggressive intervention indicated (e.g., tube feeding,

Systemic				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
				total parenteral nutrition)

Urinary				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social and functional activities	Pain or tenderness causing inability to perform basic self-care function OR hospitalization indicated
Injection Site Erythema or Redness or Induration or Swelling *Report only one*	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area AND symptoms causing no or minimal interference with usual social and functional activities	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area OR symptoms causing greater than minimal interference with usual social and functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR ulceration OR secondary infection OR phlebitis OR sterile abscess OR drainage OR symptoms causing inability to	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

Site Reactions to Injections and Infusions				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
			perform usual social and functional activities	
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalized OR itching localized to the injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social and functional activities	NA

Laboratory Values: Chemistries				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Acidosis	NA	pH ≥7.3 to <LLN	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, Low *(g/dL; g/L)*	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	NA
Alkaline Phosphatase, High	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Alkalosis	NA	pH >ULN to ≤7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to <1.5 x ULN	1.5 to <3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN

Laboratory Values: Chemistries				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Direct Bilirubin, High	NA	NA	>ULN with other signs and symptoms of hepatotoxicity	>ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Total Bilirubin, High	1.1 to <1.6 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x ULN
Calcium, High (mg/dL; *mmol/L*)	10.6 to <11.5 *2.65 to <2.88*	11.5 to <12.5 *2.88 to <3.13*	12.5 to <13.5 *3.13 to <3.38*	≥13.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*)	7.8 to <8.4 *1.95 to <2.10*	7.0 to <7.8 *1.75 to <1.95*	6.1 to <7.0 *1.53 to <1.75*	<6.1 *<1.53*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to <6 x ULN	6 to <10 x ULN	10 to <20 x ULN	≥20 x ULN
Creatinine, High *Report only one	1.1 to 1.3 x ULN	>1.3 to 1.8 x ULN OR increase to 1.3 to <1.5 x participant's baseline	>1.8 to <3.5 x ULN OR increase to 1.5 to <2.0 x participant's baseline	≥3.5 x ULN OR increase of ≥2.0 x participant's baseline
Creatinine Clearance or eGFR, Low	NA	<90 to 60 mL/min or mL/min/1.73 m^2 OR 10 to	<60 to 30 mL/min or mL/min/1.73 m^2 OR 30 to	<30 mL/min or mL/min/1.73 m^2 OR ≥50% decrease from

Laboratory Values: Chemistries				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
*Report only one		<30% decrease from participant's baseline	<50% decrease from participant's baseline	participant's baseline or dialysis needed
Glucose Fasting, High (mg/dL; *mmol/L*)	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Glucose Nonfasting, High (mg/dL; *mmol/L*)	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*)	55 to 64 *3.05 to <3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
Lactate, High	ULN to <2.0 x ULN without acidosis	≥2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
Lipase, High	1.1 to <1.5 x ULN	1.5 to <3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
Lipid Disorders Cholesterol, Fasting, High (mg/dL; *mmol/L*)	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NA
Lipid Disorders LDL, Fasting, High (mg/dL; *mmol/L*)	130 to <160 *3.37 to <4.12*	160 to <190 *4.12 to <4.90*	≥190 *≥4.90*	NA
Lipid Disorders Triglycerides, Fasting, High (mg/dL; *mmol/L)*	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to <1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium, Low (mEq/L; *mmol/L*)	1.2 to <1.4 *0.60 to <0.70*	0.9 to <1.2 *0.45 to <0.60*	0.6 to <0.9 *0.30 to <0.45*	<0.6 *<0.30*

Laboratory Values: Chemistries				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Phosphate, Low (mg/dL; *mmol/L*)	2.0 to <LLN *0.65 to <LLN*	1.4 to <2.0 *0.45 to <0.65*	1.0 to <1.4 *0.32 to <0.45*	<1.0 *<0.32*
Potassium, High (mEq/L; *mmol/L*)	5.6 to <6.0 *5.6 to <6.0*	6.0 to <6.5 *6.0 to <6.5*	6.5 to <7.0 *6.5 to <7.0*	≥7.0 *≥7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to <3.4 *3.0 to <3.4*	2.5 to <3.0 *2.5 to <3.0*	2.0 to <2.5 *2.0 to <2.5*	<2.0 *<2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to <150 *146 to <150*	150 to <154 *150 to <154*	154 to <160 *154 to <160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to <135 *130 to <135*	125 to <130 *125 to <130*	121 to <125 *121 to <125*	≤120 *≤120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to <10.0 *0.45 to <0.59*	10.0 to <12.0 *0.59 to <0.71*	12.0 to <15.0 *0.71 to <0.89*	≥15.0 *≥0.89*

*Reminder: Choose the method that selects for the higher grade.

Hematology				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)	300 to <400 *300 to <400*	200 to <300 *200 to <300*	100 to <200 *100 to <200*	<100 *<100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)	600 to <650 0.600 x 10^9 to <0.650 x 10^9	500 to <600 *0.500 x 10^9 to <0.600 x 10^9*	350 to <500 *0.350 x 10^9 to <0.500 x 10^9*	<350 *<0.350 x 10^9*
Absolute Neutrophil Count, Low (cells/mm^3; *cells/L*)	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	<400 *<0.400 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00 x LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75 x LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50 x LLN	<50 *<0.50* OR <0.25 x LLN

Hematology				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
				OR associated with gross bleeding
Hemoglobin, Low (male) (g/dL; *mmol/L*)	10.0 to 10.9 *6.19 to 6.76*	9.0 to <10.0 *5.57 to <6.19*	7.0 to <9.0 *4.34 to <5.57*	<7.0 *<4.34*
Hemoglobin, Low (female) (g/dL; *mmol/L*)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
INR, High (not on anticoagulation therapy)	1.1 to <1.5 x ULN	1.5 to <2.0 x ULN	2.0 to <3.0 x ULN	≥3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to <10.0%	10.0 to <15.0%	15.0 to <20.0%	≥20.0%
PTT, High (not on anticoagulation therapy)	1.1 to <1.66 x ULN	1.66 to <2.33 x ULN	2.33 to <3.00 x ULN	≥3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <125,000 *100.000 x 10^9 to <125.000 x 10^9*	50,000 to <100,000 *50.000 x 10^9 to <100.000 x 10^9*	25,000 to <50,000 *25.000 x 10^9 to <50.000 x 10^9*	<25,000 *<25.000 x 10^9*
PT, High (not on anticoagulation therapy)	1.1 to <1.25 x ULN	1.25 to <1.50 x ULN	1.50 to <3.00 x ULN	≥3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	<1,000 *<1.000 x 10^9*

Urinalysis				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots OR with RBC casts OR intervention indicated	Life-threatening consequences

Urinalysis				
Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

13.7. Appendix 7: Cardiovascular Safety

13.7.1. Vital Signs

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs Parameter			
	Pulse	**DBP**	**SBP**	**RR**
Abnormalities based on actual values				
Grade 1 or mild	-	≥90 mmHg-<100 mmHg	≥140 mmHg-<160 mmHg	17-20 breaths per minute
Grade 2 or moderate	-	≥100 mmHg-<110 mmHg	≥160 mmHg-<180 mmHg	21-25 breaths per minute
Grade 3 or severe	-	≥110 mmHg	≥180 mmHg	>25 breaths per minute
Grade 4	≥120 bpm	-	-	Intubation

13.8. Appendix 8: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Description		%
Able to carry on normal activity and to work; no special care needed.	Normal no complaints; no evidence of disease.	100
	Able to carry on normal activity; minor signs or symptoms of disease.	90
	Normal activity with effort; some signs or symptoms of disease.	80
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	Cares for self; unable to carry on normal activity or to do active work.	70
	Requires occasional assistance but is able to care for most of his/her personal needs.	60
	Requires considerable assistance and frequent medical care.	50
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	Disabled; requires special care and assistance.	40
	Severely disabled; hospital admission is indicated although death not imminent.	30
	Very sick; hospital admission necessary; active supportive treatment necessary.	20
	Moribund; fatal processes progressing rapidly.	10
	Dead	0

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