CONFIDENTIAL

PROTOCOL

Protocol Title: A Phase 3 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of the Combination of Moxifloxacin plus PA-824 plus Pyrazinamide after 4 and 6 months of Treatment in Adult Subjects with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis and after 6 months of Treatment in Adult Subjects with Multi-Drug Resistant, Smear-Positive Pulmonary Tuberculosis.

Protocol Number: NC-006-(M-Pa-Z)

Protocol Version: 1.0

Protocol Date: 14April2014

Protocol Name: STAND (Shortening Treatment by Advancing Novel Drugs)

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SPONSOR

I agree to the terms of this trial protocol.

Daniel E. Everitt — Signature of Senior Medical Officer

DANIEL E. EVERITT, MD — Printed Name

15 April, 2014 — Date

CO-ORDINATING INVESTIGATOR

I agree to the terms of this trial protocol. I will provide medical expertise and ensure consistency across sites for this trial and in accordance to the principals of Good Clinical Practice and local regulations.

_____ — Signature

_____ — Printed Name

_____ — Date

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CO-ORDINATING INVESTIGATOR

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Signature

16 - April - 2014

Date

Stephen H Gillespie

Printed Name

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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Protocol Number: NC-006-(M-Pa-Z)
Protocol Version: 1.0
Protocol Date: 14Apr2014
Protocol Name: STAND (Shortening Treatment by Advancing Novel Drugs)

I hereby confirm that I have read the above protocol and agree to conduct this clinical trial as outlined in the above protocol. I will provide copies of the protocol and access to all the information required to conduct the clinical trial according to the above protocol to the site personnel under my supervision. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Signature	Printed Name
Date	

Development Phase:	Phase 3
Sponsor:	Global Alliance for TB Drug Development 40 Wall Street, 24th Floor New York, NY 10005 United States of America
Sponsor Physician:	Name: Dr. Daniel E. Everitt, MD Senior Medical Officer, Clinical Development Global Alliance for TB Drug Development Address: 40 Wall Street, 24th Floor New York New York 10005 Telephone: +1 646 616 8671 Mobile: +1 484 919 0017 Email: dan.everitt@tballiance.org
Co-ordinating Investigator:	Name: Dr Stephen H Gillespie MD DSc FRCP FRCPath Sir James Black Professor of Medicine and Director of Research Address: Medical and Biological Sciences Building University of St. Andrews North Haugh, St. Andrews Fife KY 16 9TF, UK Telephone: +44 1334 461 871 Mobile: +44 788 418 2315 Facsimile: +44 1334 467 470 Email: shg3@st-andrews.ac.uk

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AREDS2	Age Related Eye Disease Study 2
ART	Anti-retroviral therapy
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
AUC (0-inf)	area under the plasma concentration time curve from zero to infinity
AUC(0-24)	area under the plasma concentration time curve from zero to end of dosing interval
BA	Bactericidal Activity
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CFU	colony forming units
(e)CRF	(electronic) Case Report Form
CL/F	Oral clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
DBP	diastolic blood pressure
DMID	Division of Microbiology and Infectious Diseases
DOTS	Directly Observed Treatment, Short Course, Internationally agreed strategy for TB control
DR	Drug Resistant
DS	Drug Sensitive
DSMC	Data Safety Monitoring Committee
E	ethambutol
EBA	Early Bactericidal Activity
ECG	electrocardiogram
ERPF	effective renal plasma flow
EWD	Early Withdrawal
FF	filtration fraction
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
H	isoniazid
HIV	Human Immunodeficiency Virus
HR	rifampicin plus isoniazid

HRZE	rifampicin plus isoniazid plus pyrazinamide plus ethambutol
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IMP	Investigational Medicinal Product
IVRS/IWRS	Interactive Voice and/or Web Response services
IUATLD	International Union Against Tuberculosis and Lung Disease
J	Bedaquiline
kg	kilogram
LDH	lactate dehydrogenase
LH	luteinizing hormone
m	Meters
M	moxifloxacin
MBD	minimum bactericidal dose
MDR	Multi-Drug Resistant
MED	minimum effective dose
MGIT	mycobacterial growth indicator tube
MIC	minimum inhibitory concentration
MITT	Modified Intent to Treat
msec	milliseconds
mL	Millilitre
min	minute
MTB	*Mycobacterium tuberculosis*
NI	non-inferior
NIH	National Institutes of Health
NLME	Non-linear Mixed Effect
Pa	PA-824
Pa_{100}	PA-824 100mg
Pa_{200}	PA-824 200mg
PD	pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PR	electrocardiographic PR interval
QRS	electrocardiographic QRS interval
QT	electrocardiographic QT interval
QTc	corrected QT interval
QTcB	QT interval corrected by Bazett's method
QTcF	QT interval corrected by Fridericia's method
QTcI	QT interval corrected for individual correction formula
QTcN	QT interval corrected for population specific correction formula

RR	electrocardiographic RR interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SOC	System organ class
SSCC	Serial Sputum Colony Counts
t	Time
$t_{½}$	apparent terminal elimination phase half-life
TB	Tuberculosis
TEAEs	treatment-emergent adverse events
T_{max}	time at which C_{max} is observed
T_{MIC}	Time over Minimum Inhibitory Concentration
TSP	TB Symptoms Profile
TTP	time to sputum culture positivity
UA	urinalysis
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
Z	Pyrazinamide

1. PROTOCOL SYNOPSIS

1.1. Synopsis

Name of Sponsor/Company:	Global Alliance for TB Drug Development
Name of Finished Products:	moxifloxacin 400 mg (M) tablets; PA-824 100 mg (Pa_{100}) tablets; PA-824 200 mg (Pa_{200}) tablets; pyrazinamide 500 mg (Z) tablets; rifampicin 150 mg plus isoniazid 75 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets (HRZE); rifampicin 150 mg plus isoniazid 75 mg combination tablets (HR).
Protocol Title:	A Phase 3 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of the Combination of Moxifloxacin plus PA-824 plus Pyrazinamide after 4 and 6 months of Treatment in Adult Subjects with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis and after 6 months of Treatment in Adult Subjects with Multi-Drug Resistant, Smear-Positive Pulmonary Tuberculosis.
Treatment Indication:	Pulmonary Tuberculosis (TB).
Trial Objective:	Assess the efficacy, safety and tolerability of: - moxifloxacin 400 mg plus PA-824 100 mg plus pyrazinamide 1500 mg regimen after 4 months of treatment, moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg regimen after 4 months of treatment, moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg regimen after 6 months of treatment in subjects with drug-sensitive (DS) pulmonary TB compared to standard HRZE treatment. - moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg regimen after 6 months of treatment in subjects with multi drug-resistant (MDR) pulmonary TB compared to $MPa_{200}Z$ treatment in DS-TB subjects.
Trial Design:	Phase 3, multicenter, open-label partially randomized clinical trial in five parallel treatment groups. Subjects with DS-TB will have a screening period of up to a maximum of 9 days, and be randomized to receive either $MPa_{100}Z$ daily for 4 months; or $MPa_{200}Z$ daily for 4 months; or $MPa_{200}Z$ daily for 6 months; or HRZE combination tablets daily for 2 months followed by HR combination tablets daily for 4 months. Subjects with MDR-TB will have a screening period of up to a maximum of 14 days, and will be assigned to receive $MPa_{200}Z$ for 6 months. All subjects will have follow-up for a period of 24 months from start of therapy. Post-trial treatment will be dependent on the subjects' status at the time they complete or are withdrawn from treatment with the investigational medicinal product regimen. Patients will either not require further treatment or will be referred to the applicable DS/MDR local community TB clinic for standard antituberculosis chemotherapy according to National TB Guidelines. A separate semen sub-trial will be performed at pre-identified sites also involved in the parent trial. A separate sub-trial protocol will be written to cover all aspects of this sub-trial.
Subject Population:	A total of up to 1,500 (dependent on the number of MDR-TB patients enrolled) male and female subjects, diagnosed with DS or MDR, smear-positive pulmonary TB aged 18 years and over. A total of 1,200 DS-TB subjects (300 per treatment arm) will be randomized. Up to or equal to 300 MDR-TB subjects will be assigned.

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Test Product, Dose and Mode of Administration:	The test product will be supplied as: • PA-824 100 mg tablets; • PA-824 200 mg tablets; • moxifloxacin 400 mg tablets; • pyrazinamide 500 mg tablets. Treatment will be administered orally once daily, with a full glass of water, for 17 or 26 weeks in the following dosing schemes: Subjects with DS-TB: • moxifloxacin 400 mg + PA-824 100 mg + pyrazinamide 1500 mg for 17 weeks or • moxifloxacin 400 mg + PA-824 200 mg + pyrazinamide 1500 mg for 17 weeks or • moxifloxacin 400 mg + PA-824 200 mg + pyrazinamide 1500 mg for 26 weeks. Subjects with MDR-TB: • moxifloxacin 400 mg + PA-824 200 mg + pyrazinamide 1500 mg for 26 weeks.
Positive Control Product, Dose, and Mode of Administration:	The control product will be supplied as: • rifampicin 150 mg plus isoniazid 75 mg plus pyrazinamide 400 mg plus ethambutol 275 mg combination tablets; • rifampicin 150 mg plus isoniazid 75 mg combination tablets. Treatment will be administered orally once daily, with a full glass of water at least 1 hour before or 2 hours after a meal, for 26 consecutive weeks to DS-TB subjects only, as follows: • HRZE Weeks 1-8 with daily dose per the subjects weight as follows: 30-39kg: 2 tablets; 40-54kg: 3 tablets; 55 – 70kg: 4 tablets; 71kg and over: 5 tablets. • HR Weeks 9-26 with daily dose per the subjects weight as follows: 30-39kg: 2 tablets; 40-54Kg: 3 tablets; 55-70 kg: 4 tablets; 71kg and over: 5 tablets.

Criteria for evaluation:

Primary Endpoint

Incidence of bacteriologic failure or relapse or clinical failure at 12 months from the start of therapy.

Abbreviated Definitions (full definitions will be described in the Statistical Analysis Plan (SAP)):

- Bacteriologic failure: During the **treatment period**, failure to **attain** culture conversion to negative status in liquid culture.
- Bacteriologic relapse: During the **follow-up period**, failure to **maintain** culture conversion to negative status in liquid culture, with culture conversion to positive status with a *Mycobacterium tuberculosis (MTB)* strain that is genetically **identical to** the infecting strain at baseline.
- Bacteriologic reinfection: During the **follow-up period**, failure to **maintain** culture conversion to negative status in liquid culture, with culture conversion to positive status with a *MTB* strain that is genetically **different from** the infecting strain at baseline.
- Clinical failure: A change from protocol-specified TB treatment due to treatment failure, retreatment for TB during follow up, or TB-related death.

Note:

- Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.
- Subjects who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit.

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Secondary Endpoints

Efficacy:

- Incidence of bacteriologic failure or relapse or clinical failure at 24 months from the start of therapy as a confirmatory analysis.
- The rate of change in time to sputum culture positivity (TTP) over time in the Mycobacterial Growth Indicator Tube (MGIT) system in sputum, represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time to be explored as a potential biomarker of definitive outcome.
- Time to sputum culture conversion to negative status in liquid culture (MGIT) through the treatment period to be explored as a potential biomarker of definitive outcome.
- Proportion of subjects with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 8, 12 and 17 weeks to be explored as a potential biomarker of definitive outcome.
- Change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, severity, drug relatedness, and seriousness, leading to early withdrawal and leading to death.
- Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
- Quantitative and qualitative measurement of ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed and change from baseline.
- QT/QTc intervals, including post baseline and change from baseline, will be categorized.
- Descriptive statistics of ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2] lens opacity classification and grading). Categorical data for lens opacity will be summarized in a frequency table for the left and right eye, respectively.
- Changes in male reproductive hormones.
- Semen analysis in a subset of male subjects. Endpoints and analysis will be described in a separate sub-trial protocol.

These data will be presented as descriptive analyses, and no inferential tests will be carried out.

Pharmacokinetics (PK):

Plasma concentrations from sparse sampling will be used to build a population PK model to evaluate the effects of baseline subject covariates on trial drug pharmacokinetics and associated bacteriological endpoints. PK samples from the Phase 2 trials with more frequent PK sampling will be used along with the PK samples in this trial to build the model.

Pharmacokinetics-Pharmacodynamics (PK-PD):

Population PK models will be developed using the pre-dose (trough) plasma concentrations of each drug in the combination drug regimen. These population PK models will be used to explore trends in the safety and efficacy data from the trial, and will be presented in a separate report to the Clinical Trial Report for this trial.

Mycobacterial Characterization:

The *MTB* isolates will be processed for:

- Speciation of the infecting organisms by molecular or antigen based test to confirm MTB;
- Minimum Inhibitory Concentration (MIC) against moxifloxacin and PA-824;
- Drug Susceptibility Testing for rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide using an indirect susceptibility test in liquid culture;
- Extraction of organismal (*MTB*) DNA for molecular strain typing.

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Statistical Methods:

A general description of the statistical methods planned to be used to analyze efficacy and safety data is outlined below. Specific details will be provided in the SAP which will be written and signed off prior to the First Patient In.

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT) and will evaluate the hypothesis that in the subjects with DS-TB in any arm of the experimental MPaZ treatment regimens the incidence of bacteriologic failure or relapse or clinical failure when the last enrolled subject has completed 12 months from the start of therapy, is non-inferior to the proportion observed in patients who are treated with the standard HRZE/HR regimen. Note the primary analysis will be restricted to those who are not isoniazid mono-resistant at baseline.

Both a Modified Intent to Treat (MITT) and a Per Protocol (PP) analysis will be conducted.

The first hypothesis to be tested will be the 6 month experimental regimen against the standard regimen. The second hypothesis to be tested will be the 200mg 4 month experimental regimen against the standard regimen. The third hypothesis to be tested will be the 100mg 4 month experimental regimen against the standard regimen. To preserve the type I error rate, the second hypothesis will only be tested if non-inferiority is demonstrated with the 6 month experimental regimen. Similary the third hypothesis will only be tested if non-inferiority of the 200mg 4 month regimen has been demonstrated. This hierarchical testing strategy means no adjustments are required for multiple comparisons. In addition, up to or equal to 300 subjects with MDR-TB will be enrolled. No formal statistical testing will be done for the subjects enrolled with MDR-TB.

Trial Timeline:

Estimated date of first subject enrolled:	Quarter 4 2014
Estimated date of last subject enrolled:	Quarter 2 2016
Estimated date of last subject completed (Month 12):	Quarter 2 2017
Estimated date of last subject completed (Month 24):	Quarter 2 2018

Total Duration of the Trial:

Approximately 4 years (18 month enrolment period for DS-TB subjects plus up to 9 days pre-treatment plus up to 6 months treatment and 24 month follow-up from start of therapy. Depending on the MDR-TB recruitment rate, enrolment into this arm may be continued after enrolment into the DS-TB arms is complete).

There will be either two/three/four database locks, data analyses and trial reports generated for this trial, depending on the MDR-TB recruitment rate:

1. When all DS-TB subject have completed 12 months follow-up from start of therapy. This will be used for submission for Market Authorization Approval.
2. When all DS-TB subjects have completed 24 months follow-up from start of therapy.
3. When MDR-TB recruitment is closed and subjects have completed 12 and/or 24 month follow up from start of therapy.

1.2. Trial Flow Chart

Period	Screening [a]	Treatment [b]															Follow-Up [b, c]					
Visit	Day (-14 (MDR)/ -9 (DS) to -1)	Day 1 (Baseline) [d]	Day 7 (Week 1)	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8 (Month 2)	Week 12 (Month 3)	Week 17 (Month 4) *4 month treatment* [e]	Week 17 (Month 4) *6 month treatment* [e]	Week 22 (Month 5)	Week 26 (Month 6) *4 month treatment* [e]	Week 26 (Month 6) *6 month treatment* [e]	Month 9	Month 12	Month 15	Month 18	Month 24	Early Withdrawal [c]
Written Informed Consent	X																					
Demography	X																					
Medical/Treatment/Smoking History	X																					
Inclusion/Exclusion	X																					
Early Morning and Spot Sputum [f, g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Status [h] **and CD4 Count** [i]	X																					
Karnofsky Score	X																					
Serum Pregnancy Test [j]	X	X								X		X				X						X
Laboratory Safety Tests	X	X	X	X		X				X	X	X				X						X
Male Reproductive Hormone Tests [k]	X	X	X	X		X				X	X	X				X						X
12-lead ECG [l]	X	X	X	X						X		X				X	X					X
Chest X-Ray [m]	X																					
TB Symptoms Profile	X	X		X		X				X		X				X		X			X	X
Patient Reported Health Status	X	X		X		X				X		X				X		X			X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination – full [n]	X	X										X				X						X
Physical Examination – limited			X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Pharmacokinetic Test [o]				X						X												
Ophthalmology Examination [p]	X													X			X					X
IMP Randomization/Assignment [q]		X																				
IMP Compliance Check [r]			X	X	X	X	X	X	X	X	X	X	X	X [e]		X						X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. **Screening:** May occur over a number of days (i.e. all screening procedures do not have to be performed on the same day). The Screening time period will be up to a maximum of 9 days for DS-TB subjects and 14 days for MDR-TB subjects. Should a site's ethics committee request that this be modified, the agreed upon time period will be implemented for that site.
b. **Visit Window Periods:** Weeks 1 to 8 ±3days; Weeks 12 – 26 ±7days; Months 9 – 24 ±14days; Early Withdrawal (EWD) Follow up ophthalmology examinations - ±14days.
c. **Follow-up Visits for EWD Subjects:** Once a subject has been permanently withdrawn from the trial, they will be required to attend Early Withdrawal, Month 12 (if not already performed) and Month 24 follow up visits. The Month 12 and 24 visits will be to collect Serious Adverse Event (SAE) information (including verification of survival) and patient reported TB outcome information only and may be telephonic, a home or a site visit. They will occur at Month 12 and/or 24 after the subjects start of treatment date. Additional visits required for ophthalmology examinations: If at EWD treatment duration is: (1) ≤ 14 days - no ophthalmology examination required; (2) from 15 days to ≤ 12weeks – ophthalmology examination required 3 months after EWD (3) > 12 weeks – ophthalmology examination required at EWD visit and 3 months after EWD. If an additional visit is required for a ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 3 months after the EWD visit date.
d. **Day 1 (baseline):** All procedures are to be completed prior to dosing.
e. **End of Treatment Visit:** The procedures performed at the End of Treatment Visit is dependent on the treatment arm. For those subjects in treatment arms with 4 months treatment, Week 17 is the End of Treatment visit, and for those patients in treatment arms with 6 months of treatment, Week 26 is the End of Treatment visit. IMP Compliance Check is not performed at the Week 22 visit for subjects who have completed treatment at Week 17.
f. **Early Morning and Spot Sputum Sampling:**
   - Days (-9 to -1)(Screening). Two spot sputum will be collected at the research site under the coaching and observation of the trial staff. The following analyses will be performed on one of these samples. The second sample is collected as a back-up sample to the first sample in case it is not possible to obtain a result/s on the first sample:
     - Direct microscopy for acid-fast bacilli;
     - Rapid test for fluoroquinolones and rifampicin resistance;
     - Extracted bacterial DNA molecular test for pyrazinamide resistance;
     - Liquid Culture (MGIT) for presence or absence of *MTB*;
     - TTP in liquid medium (MGIT).

     If the Day (-9 to -1)(Screening) spot sputum smear shows an indeterminate result or is AFB negative, the test may be repeated on a freshly collected spot sputum/s and that result used. The extracted *MTB* DNA and isolates will be stored for potential further work to validate new assay tools for a maximum of 5 years after trial closure.
   - All visits from Day 1 (baseline) up to and including Month 24, plus at any unscheduled visits. Two sputum samples (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff) will be collected. If both sputum samples at Month 2 or later are contaminated, the subject should return for an unscheduled visit(s) to give additional samples or to document that the subject is not able to produce sputum. If there is a positive culture at or after the end of treatment (Week 17 (4 month treatment arms)/Week 26 (6 month treatment arms)), the subject should return for an unscheduled visit(s) to give additional sputum samples a minimum of 7 days from the previous sample or to document that the subject is not able to produce sputum. Additional samples may be required in order to define a subjects primary outcome status as described in section 4.5.5. The following analyses will be performed on all sputum samples:
     - Liquid Culture (MGIT) for presence or absence of *MTB*;
     - TTP in liquid medium (MGIT).
g. **Mycobacteriology Characterisation Tests:**
   Performed on:
   - Day 1 (baseline) sputum sample (or screening or out to Week 4 if the baseline is contaminated or negative);
   - Positive Cultures at or after Week 17 (4 month treatment arms)/Week 26 (6 month treatment arms).

   The *MTB* isolates will be processed for:
   - Speciation of the infecting organisms by molecular or antigen based test to confirm *MTB*;
   - MIC against moxifloxacin and PA-824;
   - Drug Susceptibility Testing for rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide using an indirect susceptibility test in liquid culture;
   - Extraction of organismal (*MTB*) DNA for molecular strain typing.

   All Day 1 (baseline) *MTB* isolates and isolates from positive cultures to be stored at the local microbiology laboratory until trial closure. The extracted *MTB* DNA and isolates will be stored for potential further work to validate new assay tools for a maximum of 5 years after trial closure.
h. **HIV testing:** If an ELISA and/or Western Blot and/or Electro-Chemiluminescence based HIV test was performed within 1 month prior to trial start, it should not be repeated as long as documentation of testing method and result can be provided.
i. **CD4 count:** HIV-positive subjects only.
j. **Serum Pregnancy Test:** Women of child-bearing potential only, whether they are sexually active or not.

k. **Male Reproductive Hormone Tests:** Male subjects only.
l. **ECG:** Will be read centrally. Results from central reading of Day (-9 to -1)(screening) ECG should be used to determine eligibility.
m. **Chest X-Ray:** Chest X-ray at screening or within 1 month prior to screening as long as images and documentation of result can be provided. The investigator is responsible for its review and analysis for subject inclusion and randomisation stratification. Images will also be collected and read centrally.
n. **Physical Examination:** Height (m) will only be collected at Day (-9 to -1)(screening).
o. **PK:** Blood draw for PK done pre-dose and after ECGs. The time of the two doses prior to PK sample collection and the dose following PK sample collection will be collected. No PK samples will be collected for HRZE/HR treatment arm.
p. **Ophthalmology Examination:** Performed by an Ophthalmologist with AREDS2 training. Ophthalmology examinations may occur at any time within the window period for the applicable visit i.e. do not have to be performed on the same day as the site procedures.
q. **Investigational Medicinal Product (IMP) Randomization/Assignment:** Initial randomisation may occur once all of the screening results are available and the investigator has determined that the subject is eligible for the trial.
r. **IMP Compliance Check:** Trial medication administration will be supervised per local site practice to assure compliance to regimen. Performed at EWD if during treatment.

2. BACKGROUND INFORMATION

2.1. Tuberculosis Disease

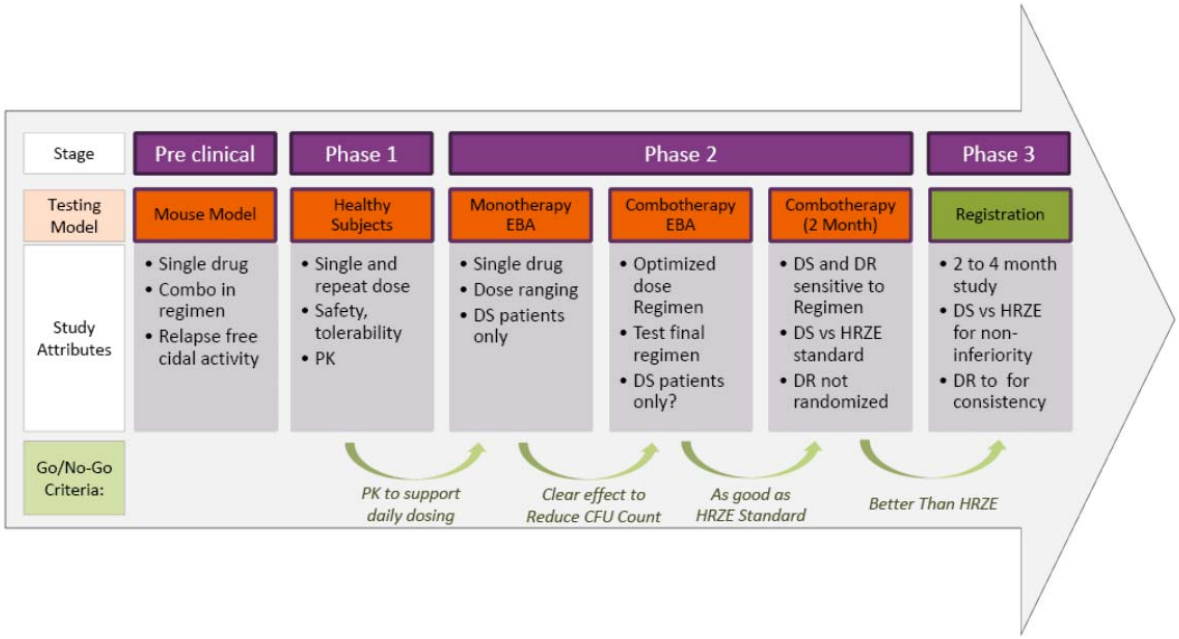
Although some progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in the developing countries of Africa, Asia and South America. TB is currently one of the top three killer infectious diseases, and there is more TB in the world today than at any other time in history. The current first-line antituberculosis agents have been in use for over 40 years and are relatively ineffective in controlling TB as a public health problem. Although the current regimens and drugs have been very successful in controlled clinical trials resulting in the permanent cure of more than 95% of trial subjects, treatment takes 6 months to complete. This, plus side effects, result in poor adherence which is particularly likely to occur after the second month of treatment. The full application of the DOTS strategy is becoming more and more difficult in the developing countries of the world that are also battling to control the HIV-epidemic. As a result of poor treatment adherence, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB are growing. Since the discovery of the rifamycins [(1)], and their introduction into standard antituberculosis regimens, very few new classes of drugs have been evaluated with a view to their registration as antituberculosis agents. On December 28, 2012 the U.S. Food and Drug Administration approved bedaquiline (J) as part of combination therapy to treat adults with multi-drug resistant (MDR) pulmonary tuberculosis (TB) when other alternatives are not available.

Following the declaration of TB as a global emergency by the World Health Organization (WHO) in 1993, there has been a resurgence of efforts to develop improved TB therapies and several promising new agents are presently in or approaching clinical evaluation. New combination regimens are desperately needed for two reasons: to shorten treatment to a duration more easily manageable by subjects and public health services, and to provide more efficacious, safer and better tolerated, affordable treatment for the growing number of subjects suffering from multidrug-resistant and extensively drug-resistant tuberculosis.

2.2. Tuberculosis Clinical Research

TB must be treated with multiple drugs to achieve maximal efficacy and prevent resistance. To transform treatment, novel TB regimens are needed. In order to telescope the time it takes to develop novel, multi-drug treatments, it is necessary to use the regimen development paradigm. This approach tests promising combinations of drugs together to find the most impactful treatment once the individual drug candidates have been tested in a robust pre-clinical program and the establishment of the individual drug candidates safety and efficacy have been evaluated. It evaluates novel combinations of TB drugs — instead of single drugs — as part of a single development program, enabling the development of novel TB drug regimens that have potential to transform treatment for drug-sensitive and drug-resistant tuberculosis. This approach offers the potential to reduce the time previously needed to develop a novel treatment regimen by up to 75%, shortening the clinical development from decades to years. The steps followed in this development model are shown in Figure 1 Between each step on the unified development pathway a decision is made as to whether to proceed.

Figure 1: Unified Drug Sensitive/Drug Resistant Regimen Development Path



Early Bactericidal Activity (EBA) Trials

EBA trials quantify the bactericidal action of antituberculosis agents alone or in combination by either studying the fall in the number of colony forming units (CFU) or measuring the Time to Positivity (TTP) in liquid culture of *M. tuberculosis* (*MTB*) present in the sputum of subjects with microscopy smear-positive pulmonary TB. EBA trials have been conducted over 2, 5, 7 and 14 days [(2)]. A review of EBA trials conducted on the key anti-TB drugs has shown the value these trials offer to demonstrate the early anti-TB effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in subjects[(3)].

8 week Bactericidal Activity (BA) Trials

EBA methodology of quantitative colony counting on solid medium has been adapted to Phase 2, 8-week TB treatment trials based on serial sputum colony counting (SSCC) or measurement of TTP liquid culture to provide a more sensitive efficacy endpoint than the previously used binary endpoint of rate of sputum conversion measured after 8 weeks of treatment. [(4, 5, 6)] Such trials are conducted to provide data on which to base the selection of treatment-shortening regimens to be advanced into pivotal registration Phase 3 evaluation trials.

2.3. MPaZ Development Path

This trial is a Phase 3 trial to evaluate the combination regimen of moxifloxacin, PA-824 and pyrazinamide (MPaZ) in subjects with pulmonary TB. The drug regimen MPaZ have been studied singularly and as combination therapy per the Unified Development Pathway with the recent successful completion of a Phase 2 8-week Bactericidal Activity Trial (NC-002-(M-Pa-Z)) and is therefore moving into the Phase 3 registration trial.

PA-824 (Pa) [(7)] is a new agent being developed for TB treatment. PA-824 is a new chemical entity and a member of a class of compounds known as nitroimidazo-oxazines, which possess significant antituberculosis activity and a unique mechanism of action [(8)]. PA-824 demonstrated in vitro activity against both drug-sensitive (DS) and MDR-TB [(9)], and in vivo activity in a mouse model of TB [(9, 10)].

Moxifloxacin (M) [(11)] is approved in most countries around the world for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and soft

tissue infections. Clinical trials have been carried out for a number of additional indications (urinary tract infections, pelvic infections, pharyngitis/tonsillitis, and tuberculosis). Moxifloxacin is an 8-methoxyquinolone whose oral formulation (which will be used in this trial) has enhanced activity against Gram-positive pathogens, and anaerobes while retaining useful activity against Gram-negative organisms. Moxifloxacin is not metabolized by nor induces the cytochrome P450 system, thus the risk of clinically relevant drug interactions is reduced. It has a positive safety profile within the fluoroquinolone class at the approved daily dose of 400 mg.

Pyrazinamide (Z) [(12)] is an approved anti-tuberculosis agent which is indicated for the initial treatment of active tuberculosis in adults and children when combined with other antituberculosis agents and contributes significantly to the sterilization of lesions and thus treatment shortening [(13)]. Pyrazinamide is the pyrazine analogue of nicotinamide.

This trial will be conducted in accordance with the Protocol, International Good Clinical Practice (GCP) Guidelines, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirement(s).

2.3.1. Individual Medicinal Products

2.3.1.1. PA-824 Development

Preclinical Trials

The nonclinical program for PA-824 completed to date included *in vitro* and *in vivo* investigations of the primary pharmacologic activity in models of TB; secondary and safety pharmacology trials; *in vitro* and *in vivo* ADME trials; and toxicology trials, including 14-day to 6-month repeat-dose toxicology trials, Segment I and Segment II reproductive toxicology trials, and genotoxicity investigations of PA-824 and its metabolites [(7)].

Results of nonclinical *in vitro* investigations [(14)] supported the activity of PA-824 against both drug-sensitive and drug-resistant *MTB* strains. Findings of *in vivo* experiments using a mouse model of TB further demonstrated activity for PA-824, both as a monotherapy and in a variety of combinations with existing antibiotics. The results of these nonclinical trials suggest that (1) regimens involving PA-824 that may be useful in treating TB when given for shorter durations than the current standard of 6 months or longer; and (2) PA-824 may be able to serve as a replacement for either isoniazid or rifampin in standard first-line TB treatment, or for both isoniazid and rifampin when combined with moxifloxacin, or in other regimens not containing these two drugs.

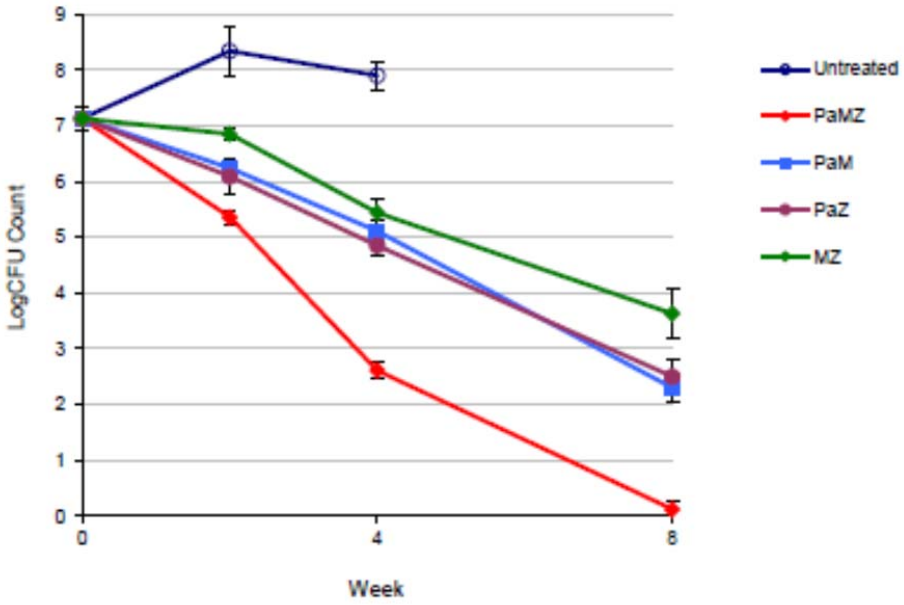
Mycobacteriology Results Summary

In vitro trials have demonstrated that the minimum inhibitory concentration (MIC) of PA-824 against a variety of drug-sensitive *MTB* isolates is similar to the MIC of isoniazid (MIC of PA 824, ≤0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). PA-824 was efficacious *in vitro* against drug-resistant clinical isolates of *MTB*, with MIC values ranging from 0.03 to 0.53 µg/mL. The minimum effective dose (MED) of PA-824 was 12.5 mg/kg/day in a mouse model of TB. The MED is defined as the lowest dose able to prevent the development of macroscopic lung lesions and splenomegaly. The minimum bactericidal dose (MBD) was 100 mg/kg/day in the same mouse model. The MBD is defined as the lowest dose able to reduce the lung TB CFU counts by 99%. The magnitude of CFU reduction by PA-824 at this dose is similar to that seen with the highest dose of isoniazid tested in the same trial (25 mg/kg/day). PA-824 was efficacious *in vitro* against drug-resistant clinical isolates of TB, with MIC values ranging from 0.03 to 0.53 µg/mL.

In a dose fractionation trial using an *in vivo* mouse model of active TB, PA-824 exhibited time-dependent bactericidal activity with a maximum observed bactericidal effect of 0.1 log CFU/day over 24 days. In this trial, lung CFU counts were strongly correlated with the free drug T_{MIC} (cumulative percentage of dosing interval that drug concentration exceeded the MIC under steady-state exposure conditions). Similar results were seen with PA-824 in an *in vivo* mouse model against persistent *MTB* strains.

Experiments employing a mouse model of TB indicated that PA-824, when administered in combination with a subset of current first-line TB drugs, may have the potential to (1) shorten the duration of TB chemotherapy for drug-susceptible TB by two months or more, and (2) act in concert with moxifloxacin to replace both rifampin and isoniazid in standard therapy or other anti-mycobacterial agents, yielding a regimen that could prove valuable for treating both DS- and MDR-TB (Figure 2).

Figure 2: Mean Lung Log10 CFU Counts (±SD) After One Month of Treatment in a Murine Model of Tuberculosis. [15]



Abbreviations: CFU = colony-forming units; M = moxifloxacin; Pa = PA-824; SD = standard deviation; Z = pyrazinamide.

Safety Results Summary

The non-clinical safety evaluation of PA-824 includes pharmacology, pharmacokinetics, toxicology and metabolism trials that were conducted in accordance with current International Conference on Harmonization (ICH) guidelines.

Metabolite analyses in rats, monkeys, and humans indicate an overall similar metabolic profile in these species with some differences among minor metabolites. These trials have confirmed that rats and monkeys are appropriate species for the toxicology program.

PA-824 was negative in all genotoxicology trials performed. One of its metabolites (M50) that is found in rat, monkey, and human plasma was positive in a screening Ames assay. M50 is not a major metabolite in humans and the exposure relative to parent drug is higher in the rat (24%) and monkey (18%) than in humans (6%).

PA-824-induced effects in respiratory, CNS, and cardiovascular safety pharmacology trials were generally mild and reversible; effects were most prominent at 450 mg/kg/day.

PA-824 inhibited human ether-à-go-go-related gene current with 50% inhibitory concentration (IC_{50}) values of approximately 6.2 µg/mL. Following a single PA-824 dose of 450 mg/kg in monkeys, QTc interval prolongation ranged from 21 to 36 msec using Fridericia's formula (QTcF) to correct for heart rate. Coadministration of PA-824 with moxifloxacin in the monkey or with bedaquiline in the dog did not result in any greater effect on the QT

interval than with either agent alone. After repeated daily doses, the QTc interval in the monkey was prolonged at PA-824 doses of ≥150 mg/kg/day.

Repeat-dose toxicology trials with PA-824 have been conducted in male and female rats (14 days to 6 months) and in male and female monkeys (7 days to 3 months). In all trials, dose-dependent reduced food consumption and reduced weight gain or weight loss were noted. In addition, testicular atrophy was observed in rats while cataracts were observed by indirect ophthalmoscopy in both rats and monkeys. In general, toxicity in both rat and monkey was significantly greater when exposures exceeded approximately 300 µg•hr/mL in the 14-day trials and approximately 200 µg•hr/mL in the 3-month trials.

Reproductive toxicology trials show that PA-824 is not teratogenic in rats or rabbits. In the rat fertility trial, dose-dependent reduced fertility rates, due to decreased sperm numbers and decreased motility, were observed at doses of 30 mg/kg and greater. This effect was partially reversible. As in the 3-month rat toxicology trial, irreversible testicular lesions were not observed at 30 mg/kg, only at 100 and 300 mg/kg.

To more fully characterize the cataract and male reproductive system findings, a 3-month monkey trial in sexually mature males (0, 50, 150, 300 mg/kg/day) and a 6-month rat trial (0, 30, 100, 300 mg/kg) in males and females were conducted. Ocular assessments were conducted in a much more careful and systematic manner than in the initial 3-month toxicology trials described above. In each of the later trials, all ophthalmologic examinations were conducted by a single ophthalmologist, using both indirect ophthalmoscopy and slit-lamp biomicroscopy. Animals were screened before dosing to ensure no animal had cataracts at baseline, and then monthly during dosing and recovery. In this monkey trial, although similar drug exposures were attained as in the original 3 month monkey trial, no cataracts or testes effects (semenology, organ weights, histopathology, or hormones [testosterone, follicle-stimulating hormone, Inhibin B]) were observed at any point during dosing or during a 20-week recovery period. PA-824 does not appear to cause cataracts or testicular toxicity in monkeys. In the 6-month rat trial, PA-824 caused irreversible cataracts at 100 mg/kg from Day 118 of the trial in males and females. In contrast to the original 3-month rat report, rats in this more carefully conducted trial developed cataracts while on drug but not during recovery. The NOAEL was 30 mg/kg for cataracts and 10 mg/kg for testicular toxicity. Rats that developed cataract and testicular toxicity also experienced marked decreases in body weight gain and food consumption. The AUC safety multiples (relative to the exposures obtained at the anticipated clinical dose of 200 mg/day) for cataract are ~1.5x in the rat; in the monkey at the highest dose tolerated, where there were no cataracts in the second well conducted trial, the multiple is at least 3.7x.

To summarize, cataracts have been detected in multiple animals from two similar rat trials at mid-to-high doses. In contrast, the finding of cataracts in one monkey trial could not be confirmed in a follow-up trial. Thus, both cataracts and the testicular effects appear to be species-limited.

Clinical Trials

Phase 1 Healthy Volunteer Clinical Trials

PA-824 has been tested in 10 single- and multi-dose Phase I trials with healthy adult male and female subjects, with 289 subjects receiving single oral doses ranging from 50 to 1500 mg and multiple oral doses ranging from 50 to 1000 mg/day given for up to 14 days (Table 1). These Phase I trials have evaluated the safety, tolerability, and pharmacokinetics (PK) of PA-824 after single and repeated doses.

Table 1: **Summary of Phase 1 PA-824 Clinical Trials**

Trial	Design	Trial Treatments (Treatment Duration)	No. Subjects Enrolled and Treated	Key Safety/Efficacy Findings
CL-001	Double-blind, placebo-controlled, dose-escalating, PK and safety trial	PA-824: 50, 250, 500, 750, 1000, 1250, 1500 mg and Placebo (Single dose after overnight fast)	40 (n=4 - 6/dose group) 13	• Well tolerated; no dose-limiting TEAEs or effects on ECG, vital signs, or PE. • Moderate serum creatinine elevation
CL-002	Double-blind, placebo-controlled multiple-dose, escalating, PK and safety trial	PA-824: 200, 600, 1000 mg/day Placebo (7 days, once daily dosing after overnight fast)	18 (n=6/dose group) 6	• Well tolerated at doses <1000 mg/day. Dosing terminated for 1000 mg/day dose group. • After 5 days dosing at 1000 mg/day, progressive moderate creatinine elevation: reversed during 7-day washout period. • No consistent effect on BUN. • A planned 1400-mg cohort not enrolled.
CL-003	Open-label, single-dose, food effects and safety	PA-824: 1000 mg (Single dose; dosing within 30 minutes of a high-fat, high-calorie meal or following an overnight fast; 8-day washout separated each dose)	16	• Well tolerated; no dose-limiting TEAEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • TEAEs affecting more than one subject occurred more frequently after dosing in the fed condition than the fasted condition, and more frequently among women than men. • Bioavailability 3.5- fold higher when PA-824 was administered in fed state compared with fasted state.
CL-004	Open-label, single-dose, ADME and safety	PA-824: ~860 mg, oral suspension [benzyl-^{14}C] PA-824 (Single dose after overnight fast)	6	• Well tolerated; no dose-limiting TEAEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • ~91% of dose recovered (~65% in urine; ~26% in feces) Plasma: parent drug and one major metabolite. Urine: little or no parent drug; multiple major metabolites. Feces: minimal unchanged parent drug; numerous low-abundance metabolites.
CL-005	Double-blind, placebo-controlled, multiple-dose, renal safety	PA-824: 800, 1000 mg Placebo (8 day, once daily dosing after overnight fast)	31 (n=21 for 800 mg n=10 for 1000 mg) 16	• Well tolerated; no dose-limiting TEAEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • Serum/plasma creatinine levels increased significantly (up to ~40%) during treatment; reversed during 7-day washout period. • No effect during treatment on GFR, ERPF, FF, BUN or UA.

Trial	Design	Trial Treatments (Treatment Duration)	No. Subjects Enrolled and Treated	Key Safety/Efficacy Findings
CL-006	Open-label, multiple-dose, drug interaction trial with midazolam	PA-824: 400 mg (Midazolam 2 mg on Day 1; PA-824 on Days 4 to 16 after overnight fast; and PA-824 + midazolam 2 mg on Day 17)	14	• Well tolerated; no dose-limiting TEAEs. • For midazolam, the geometric mean ratio of Day 17 (midazolam+PA-824) vs. Day 1 (midazolam alone) for C_{max} was 0.84 and $AUC_{0\text{-}inf}$ was approximately 0.85 (0.84 [90% CI: 0.75, 0.93] and 0.85 [90% CI: 0.74, 0.97], respectively). • For the 1-hydroxy midazolam metabolite, the corresponding geometric mean ratio was 1.05 for C_{max} and 1.13 for $AUC_{0\text{-}inf}$.
CL-008	Open-label, single-dose, ADME and safety	PA-824: ~1100 mg, oral suspension [imidazooxazine-14C]PA-824 (Single dose after overnight fast)	6	• Well tolerated; no dose-limiting TEAEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • ~91% of dose recovered (~53% in urine; ~38% in feces). Plasma: parent drug. Urine: little or no parent drug; multiple major metabolites. Feces: unchanged parent drug and numerous low abundance metabolites.
CL-009	Open-label, single-dose, food effects and safety	PA-824: 50 and 200 mg (Single dose; dosing within 30 minutes of a high-fat, high-calorie meal or following an overnight fast; 8-day washout separated each dose)	32 (n=16/dose group	• Well tolerated; no dose-limiting TEAEs. • In the presence of high fat, high calorie diet, C_{max} and AUC of the 50-mg dose were increased 1.25-fold and 1.45-fold, respectively, compared to fasted state, whereas for the 200-mg dose, C_{max} increased by 1.73-fold and AUC increased by 1.88-fold when dosed with a meal.
DMID 10-0058	Randomized, double-blind, placebo and positive control, 5-period, single dose crossover, single center, thorough QT	A: Placebo B: PA-824 400 mg C: PA-824 1000 mg D: Moxifloxacin 400mg E: PA-824 400 mg + moxifloxacin 400mg All treatments as a single dose	74	• The upper limit of the 90% CI for QTcI did not exceed 4.4 ms for the 400-mg dose or 6.1 ms for the 1000-mg dose, and both were well below 10 ms. PA-824 400 mg plus moxifloxacin 400 mg exceeded 10 ms at multiple time points during the observation period. This was similar to the effect observed with moxifloxacin administered alone. • A 2.5-fold increase in PA-824 dose from 400 mg to 1000 mg resulted in an approximate 2-fold increase in AUC and a 1.8-fold increase in Cmax. Across this dose range, the rate of elimination was independent of dose and the terminal half-life was approximately 18.5 hours. • Median T_{max} was similar for both PA-824 doses and occurred approximately 4.5 to 5 hours post-dose. • The PK of PA-824 was not affected by the co-administration of moxifloxacin.

Trial	Design	Trial Treatments (Treatment Duration)	No. Subjects Enrolled and Treated	Key Safety/Efficacy Findings
A5306	Open label, multi- center trial, completed in 3 sequential phases (Arms) with crossover within each Arm. Drug drug interaction.	Arm 1: PA-824 200mg QD for 1 wk efavirenz 600mg QD for 2 wks PA-824 + efavirenz QD for 1 wk	18	Arm 1: • The median data and geometric mean ratios revealed that overall, and in both Extensive and Intermediate metabolizers, PA-824 $AUC_{0\text{-}24h}$, C_{min}, C_{max}, and $T_{1/2}$ were significantly lower, and CL/F was significantly greater, when PA-824 was administered with efavirenz. However, PA-824 Tmax was not changed when co-administered with efavirenz. • Overall, there were no significant changes in any of the measured efavirenz PK parameters when efavirenz was administered alone or co-administered with PA-824. • No grade 2 or higher chemistry, hematology, or QTc events were observed. No graded diagnoses were observed on study. No grade 3 or higher signs and symptoms were reported.

Phase 1 Results Summary

In these trials, PA-824 has been administered in doses ranging from 50 to 1500 mg as 50 or 200 mg tablets or as an oral suspension. PK parameters have largely been consistent in each trial and can be summarized as follows.

PA-824 is moderately rapidly absorbed, with median T_{max} values across subjects and dose levels ranging from 4 to 7 hours.

The mean half-life for elimination ($t_{½}$) across subjects and dose levels was approximately 16 - 25 hours.

Exposure increased approximately linearly but less than dose-proportionally, with increasing doses up to approximately 600 – 1000 mg, while higher doses achieved minimal additional increases in either C_{max} or AUC.

Radioprofiling and metabolite identification work have been completed on samples from the two human trials as well as from analogous work in rat and monkey using both radiolabeled PA-824 preparations. The metabolism of PA-824 proceeds via a combination of reductive metabolism (~20 – 25% of the dose) and oxidative metabolism (remainder of the characterized metabolites). The metabolic profile of PA-824 *in vivo* was qualitatively similar in the three species, with quantitative differences being minor. No human unique metabolites were detected and there is no one single metabolic path that can be considered major. Furthermore, there are no major metabolites in human plasma.

Trial PA-824-CL-006, a drug-drug interaction trial with midazolam to assess the extent of CYP3A inhibition by PA-824, results indicate that dosing of PA-824 400 mg once daily for 14 days did not have a major effect on the exposure of midazolam or its major metabolite 1-hydroxy midazolam. For midazolam, the geometric mean ratio of Day 17 (midazolam+PA-824) vs. Day 1 (midazolam alone) for C_{max} was 0.84 and AUC was 0.85. For the 1-hydroxy midazolam metabolite, the corresponding geometric mean ratio for C_{max} was 1.05 and AUC was 1.11. The data suggests that PA-824 does not cause clinically significant drugs interactions with drugs metabolized by CYP3A. No drug-drug interaction is anticipated between PA-824 and either pyrazinamide or moxifloxacin.

Trial PA-824-CL-009, a food effects trial using lower doses of PA-824 (200 mg and 50 mg), results indicate that the food effect observed is dependent on the PA-824 dose administered. When a single dose of PA-824 was administered with a high fat, high calorie meal, C_{max} and AUC of the 50 mg dose increased 1.40-fold and 1.45-fold respectively, whereas for the 200 mg dose, C_{max} increased 1.76-fold and AUC increased 1.88-fold.

ACTG Trial A5306, a three-arm, three-period, crossover trial in healthy HIV-1 uninfected volunteers investigated potential interactions between steady-state PA-824, efavirenz, ritonavir-boosted lopinavir, or rifampin. Results indicate that concomitant dosing of PA-824 at 200mg with all three drugs reduced PA-824 concentrations by 35% (AUC_{0-24}; 0.65ng*h/mL), 17% (AUC_{0-24}; 0.83ng*h/mL) and 66% (AUC_{0-24}; 0.34 ng*h/mL) respectively for efavirenz, ritonavir-boosted lopinavir and rifampin. These effects on PA-824 exposure are not thought to have a clinically meaningful impact requiring a dose adjustement for PA-824 when administered at the daily doses of 100 mg or 200 mg.

DMID Trial 10-0058, was a double-blind, randomized, single-center, 5-period crossover trial assessing the effects of single oral doses of 400mg and 1000mg of PA-824 and 400mg of PA-824 plus 400mg of moxifloxacin on QT interval in healthy volunteers. Results indicate that a single PA-824 dose of either 400mg or 1000mg does not cause QT interval prolongation to a level of clinical concern. The effect of PA-824 400mg plus moxifloxacin on QTcI was similar to the effect of moxifloxacin administered alone.

These Phase I Trials demonstrated the safety, tolerability, and PK of orally administered PA-824 after single and repeated doses.

Phase 2 Monotherapy EBA Clinical Trials

In the Phase 2 Monotherapy EBA trials, oral doses of 50 to 1200 mg/day PA-824, as a single agent, were administered for 14 days to 122 subjects (Table 2).

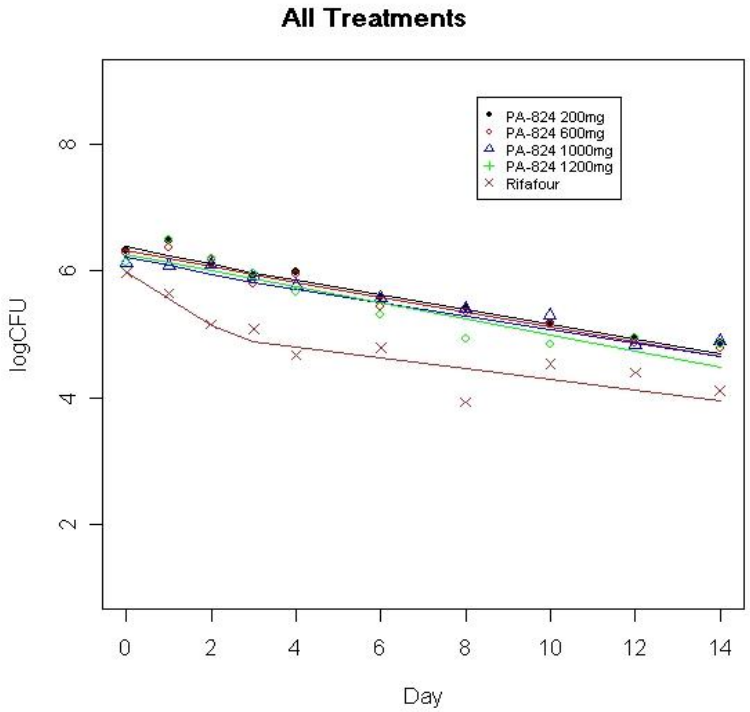
Table 2: **Summary of Phase 2 Monotherapy EBA PA-824 Clinical Trials**

Trial	Design	Trial Treatments (Treatment Duration)	No. Subjects Enrolled and Treated	Key Safety/Efficacy Findings
CL-007	Partially double blinded (blinded as to PA-824 dose), multiple-dose, EBA, safety, and PK	PA-824: 200, 600, 1000, 1200 mg Rifafour e-275 (14 days, once daily dosing after overnight fast)	61(n=15 or 16/dose group) 8	• PA-824 treatment produced a measurable decrease in log CFU, with the magnitude of effect equivalent for all doses. • Well tolerated overall. Two SAEs (hemoptysis) occurred (one on PA-824 and led to discontinuation); both were considered unrelated to trial treatment. • No dose-limiting laboratory findings or clinically significant effects on vital signs or PE noted. Clinically significant, possibly treatment-related conduction disorder AEs reported in 2 subjects in PA-824 groups and 1 in Rifafour group.

Trial	Design	Trial Treatments (Treatment Duration)	No. Subjects Enrolled and Treated	Key Safety/Efficacy Findings
CL-010	Partially double blinded (blinded as to PA-824 dose), multiple-dose, EBA, safety, and PK	PA-824: 50, 100, 150, 200 mg Rifafour e-275 (14 days, once daily dosing after overnight fast)	61(n=15 or 16/dose group) 8	• PA-824 treatment produced a measurable decrease in log CFU with some evidence of dose dependence. • Well tolerated overall. Two SAEs (pneumonia, pneumothorax [led to discontinuation]) in PA-824 groups; both were considered unrelated to trial treatment. • No dose-limiting laboratory findings or clinically significant effects on ECGs, vital signs or PE noted.

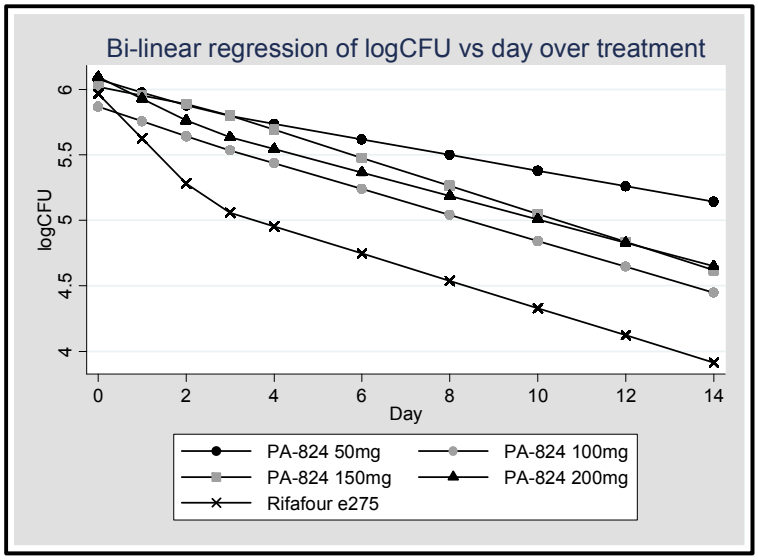
The efficacy data from trial PA-824-CL-007 [16] indicated that all doses of PA-824 including the lowest dose, 200 mg, produced a measurable and equivalent decrease in sputum CFU counts over the 14-day treatment period; no difference could be discerned among the PA-824 treatment groups (Figure 3).

Figure 3: PA-824-CL-007 Mean Group logCFU Values Over Time



Trial PA-824-CL-010 [17] results indicated that PA-824 treatment resulted in a measurable dose-dependent mycobactericidal activity, with the 50 mg dose demonstrating less activity than the 100, 150 and 200 mg doses, which were all equivalent (Figure 4). The results of the 200 mg and Rifafour arms were also consistent with the results for those same dose arms in trial PA-824-CL-007, indicating these EBA trials are highly reproducible when conducted at these clinical and laboratory sites, and supporting the choice of 200 mg orally once per day, as the clinical dose of PA-824.

Figure 4: Mean logCFU Values Over Time with Fitted Bi-Linear Regression, Trial PA-824-CL-010.



Abbreviation: CFU = colony-forming unit.
* Day 0 = (Day -2 + Day -1)/2 = baseline measurement.

Phase 2 Clinical Safety Results

See section 2.4 for the summary of all Clinical Safety Results.

2.3.1.2. Moxifloxacin Development

Moxifloxacin has been approved in most countries around the world for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and soft tissue infections. An extensive clinical program supports the safety and efficacy of 400 mg moxifloxacin given once daily for 5 to 21 days in adults for the above specified indications. Moxifloxacin has been used extensively in the treatment of MDR-TB, and has been employed in clinical trials for periods of between eight weeks an four months without any evidence of clinical toxicity [(5, 18, 19)].

For more detailed information, please refer to the Investigator Brochure (IB) for Moxifloxacin [(11)].

Moxifloxacin is commonly used as second line therapy for TB in subjects (e.g., MDR- TB), and has also been evaluated in several clinical trials of subjects with TB, including four 8-week treatment period phase 2b trials (Table 3) .

Table 3: Summary of Phase 2 trials in which moxifloxacin were administered as part of a four-drug regimen during the intensive phase of treatment (total treatment duration: 2 months)

Trial	Sponsor	Design	Objective[a]	Subjects N	Countries	Status
Study 27	Tuberculosis Trials Consortium (TBTC)	Randomized, double-blind, controlled	To compare the sputum culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using the standard 4-drug regimen HRZE with a standard regimen with M replacing E.	336	USA, Canada, Uganda, South Africa	Completed

Trial	Sponsor	Design	Objective[a]	Subjects N	Countries	Status
OFLOTUB Study	South African Medical Research Council	Randomized, Open label, Controlled	To compare the bactericidal activities of regimens where gatifloxacin, M, and ofloxacin were substituted for E in the 2-month initial phase of standard TB treatment with HRZE.	217	South Africa	Completed
Johns Hopkins (FDA orphan drug) Study	Johns Hopkins University & FDA orphan drugs program	Randomized, double-blind, Controlled	To compare the sputum culture conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE) with a regimen with M replacing E (HRZM).	170	Brazil	Completed
Study 28	Tuberculosis Trials Consortium (TBTC) /CDC	Randomized, double-blind, Controlled	To compare the culture-conversion rate at the end of the 4-drug (intensive) phase of therapy using a standard 4-drug regimen (HRZE 5 days per week) with a regimen with M replacing H (MRZE 5 days per week).	433	USA, Canada, Brazil, Spain, Uganda, South Africa	Completed
REMox-TB	TB Alliance. Bayer, British MRC, University College London	Randomised placebo – controlled, double blind	To compare six months standard treatment versus four months standard treatment with moxifloxacin substituted for ethambutol, versus four months standard treatment third group received moxifloxacin substituted for isoniazid to see whether the shorter treatment is as effective as the standard six month treatment.	1,931	China, India, Kenya Malaysia, Mexico, Tanzania, Thailand, South Africa, Zambia.	Completed. Data currently analyzed.

2.3.1.3. Pyrazinamide Development

Pyrazinamide is an approved anti-tuberculosis agent which is indicated for the initial treatment of active TB in adults and children when combined with other antituberculosis agents and contributes significantly to the sterilization of lesions and thus, treatment shortening [(13)]. Pyrazinamide is the pyrazine analogue of nicotinamide.

2.3.2. Combination Development

2.3.2.1. Phase 2 Combotherapy EBA Clinical Trials

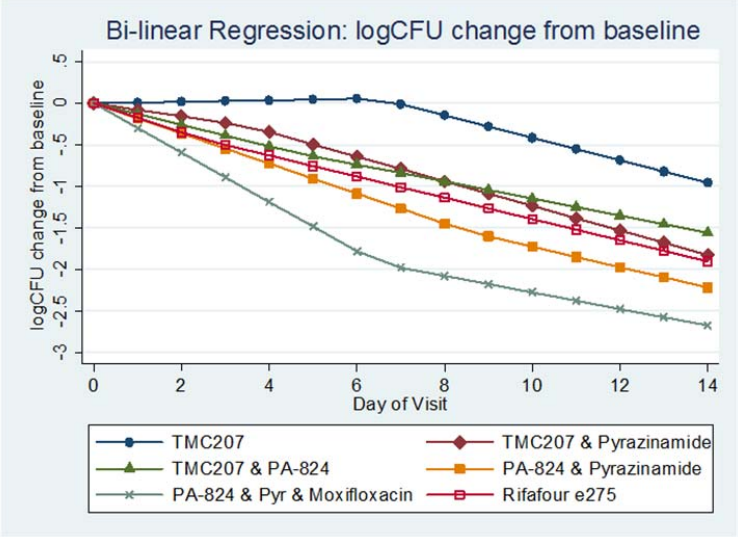
The monotherapy EBA trials demonstrated that PA-824 has EBA and it was determined therefore to take PA-824 200mg into a combination EBA trial. In Trial NC-001-(J-Pa-M-Z) an oral dose of 200 mg/day was given in combination with other anti-tuberculosis agents (Table 4).

Table 4: **Summary of Phase 2 Combotherapy EBA JMPaZ Clinical Trial**

Trial	Design	Trial Treatments (Treatment Duration)	No. Subjects Enrolled and Treated	Key Safety/Efficacy Findings
NC-001	Partially double blinded (blinded for PA-824 + pyrazinamide or PA-824 + pyrazinamide + moxifloxacin; or bedaquiline alone or plus pyrazinamide), multiple-dose, EBA, safety, and PK	• PA-824 200 mg + bedaquiline • PA-824 200 mg + pyrazinamide • PA-824 200 mg + pyrazinamide + moxifloxacin • bedaquiline alone • bedaquiline + pyrazinamide • Rifafour e-275 (14 days, once daily dosing after overnight fast)	15 15 15 15 15 10	• All PA-824 combinations produced a measurable decrease in log CFU, with the rank ordering for activity being PA-824 + pyrazinamide + moxifloxacin combination > PA-824 + pyrazinamide > PA-824 + bedaquiline. • Well tolerated overall, with suggestion of higher frequency of TEAEs leading to discontinuation in PA-824 + pyrazinamide + moxifloxacin group (20% vs 6.7% in PA-824 + pyrazinamide or PA-824 + bedaquiline groups). • Two SAEs (worsening pulmonary TB, neurocysticercosis) in PA-824 groups; both were considered unrelated to trial treatment.

The greatest efficacy was seen for the MPaZ treatment group (Figure 5).

Figure 5: **Mean logCFU Over Time (Fitted Bi-Linear Regression), Trial NC-001-(J-M-Pa-Z).**



2.3.2.2. Phase 2b 8 week Bactericidal Activity Trials

Trial NC-001-(J-M-Pa-Z) demonstrated the substantial bactericidal activity of the MPaZ regimen, and it was decided to take this combination into a phase 2b 8 week Bactericidal Activity trial, trial NC-002-(M-Pa-Z) (

Table 8) to select the treatment-shortening regimen to be advanced into pivotal registration Phase III evaluation trials.

This trial has recently completed and was a multicenter open-label partially randomized clinical trial with four treatment groups, as follows:

DS-TB: Patients were randomized to receive:

- $MPa_{100}Z$ or
- $MPa_{200}Z$ or
- Rifafour e-275 (standard H-R-Z-E therapy included as a control arm for the DS treatments and for the lab methodology).

MDR-TB: Patients were assigned to receive $MPa_{200}Z$.

A subset of patients from each treatment group was included in a 14 day inpatient EBA sub-trial. All patients received 8 weeks of treatment and returned for follow-up visits at 2 and 12 weeks after trial treatment completion. The trial population included a total of up to 230 male and female newly diagnosed patients with DS or MDR, smear positive pulmonary tuberculosis aged 18 to 65 years (inclusive). The primary efficacy endpoint was the rate of change in the logarithm CFU count over 8 weeks of treatment analyzed by a Join Bayesian Non-linear Mixed Effect (NLME) regression. Secondary efficacy endpoints included time to sputum culture conversion using data from weekly cultures through 8 weeks (separately, on solid and liquid media), and the rate of change in logarithm TTP through 8 weeks in the Mycobacterial Growth Indicator Tube (MGIT) system in sputum over 8 weeks in subjects, analyzed by a Join Bayesian NLME regression.

Preliminary data analyses of the trial indicate that a total of 207 subjects were enrolled, as follows:

- DS-TB $MPa_{100}Z$: 60 enrolled, 55 completed 8 weeks treatment;
- DS-TB $MPa_{200}Z$: 62 enrolled, 54 completed 8 weeks treatment;
- DS-TB Rifafour e-275: 59 enrolled, 54 completed 8 weeks treatment;
- MDR-TB $MPa_{200}Z$: 26: enrolled, 21 completed through too day 14; 10 completed 8 weeks treatment. (Note: 16 MDR subjects were withdrawn as late-exclusions (*MTB* resistant to pyrazinamide determined in culture after enrollment in the trial))

The median age was 28 years, 65% were male, and 19.5% of the subjects were HIV-infected.

For the primary endpoint, subjects in the $MPa_{200}Z$ arm had a statistically significantly greater decline in the log CFU count over the 8 weeks than the subjects in the HRZE arm. The estimates of the mean serial log CFU counts over time are shown graphically in Figure 6 and quantitatively in Table 5.

Figure 6: Trial NC-002-(M-Pa-Z) Estimates of Mean Serial log(CFU) Count Over Time Joint Bayesian NLME Regression

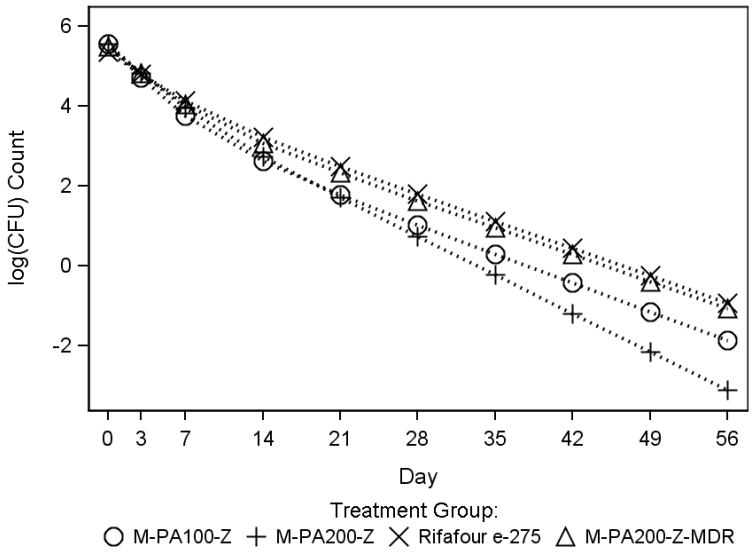


Table 5: **Trial NC-002-(M-Pa-Z) Estimates of Mean Serial log(CFU) Count Over Time Joint Bayesian NLME Regression**

Trial Arm	Log CFU Reduction per Day over 56 Days
$MPA_{200}Z$* (DS) (N=56)	0.155 CI [0.133; 0.178]
$MPA_{100}Z$ (DS) (N=54)	0.133 CI [0.109; 0.155]
$MPA_{200}Z$ (MDR) (N=9)	0.117 CI [0.070; 0.174]
Rifafour (HRZE) (DS) (N=54)	0.112 CI [0.093; 0.131]

* Statistically significant difference between M-PA_{200}-Z and Rifafour (p = 0.043)

For the secondary endpoint of conversion rates at 8 weeks all groups had a higher rate of conversion of sputum to a negative culture for *MTB* on solid culture than on liquid culture. This was expected and consistent with prior trials, as liquid culture more readily supports growth of small inoculums of *MTB* and isolates that are slow growing. Subjects in both of the MPaZ DS groups had substantially and statistically significantly greater rates of conversion to negative growth in liquid culture than the group on Rifafour (HRZE) as noted in Table 6.

Table 6: **NC-002-(M-Pa-Z) Eight Week Culture Conversion to Negative in Solid and Liquid Culture**

Trial Arm	Conversion to Negative (%)	
	Solid	Liquid
$MPA_{200}Z$ (DS) (N=54)	94.3	71.4*
$MPA_{100}Z$ (DS) (N=55)	82.9	65.7*
$MPA_{200}Z$ (MDR) (N=9)	62.5	50.0
Rifafour (HRZE) (DS) (N=54)	87.5	37.8

*Significant difference compared to Rifafour for liquid culture only (p<0.05)

A secondary endpoint evaluated the logTPP in the MGIT liquid culture system. Prior trials have showed a close correlation between the increase in TTP over time in liquid culture and decrease in CFU over time on solid culture. As the bacterial load of MTB in the sputum decreases over time, the TTP increases. A maximum incubation time of 42 days is considered to be a negative culture. Figure 7 and

Table **7** show the estimates of the mean serial log TTP over time graphically and quantitatively. The results of this analysis are consistent with the changes in log CFU over time, although there were no statistically significant differences between the MPaZ and the Rifafour (HRZE) treatment arms.

Figure 7: **Trial NC-002-(M-Pa-Z) Estimates of Mean Serial log(TTP) Over Time Joint Bayesian NLME Regression**

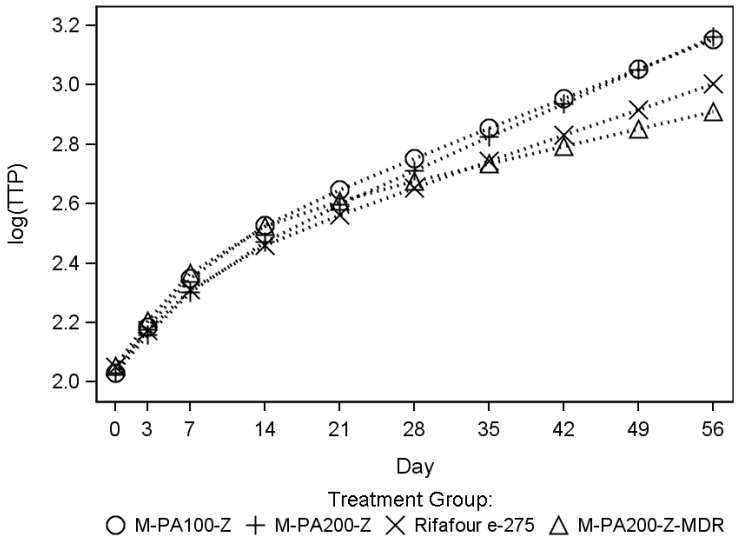


Table 7: Trial NC-002-(M-Pa-Z) Estimates of Mean Serial log(TTP) Over Time Joint Bayesian NLME Regression

Trial Arm	Log TTP increase per Day
$MPA_{200}Z$ (DS) (N=57)	0.020, 95% CI [0.016; 0.024]
$MPA_{100}Z$ (DS) (N=55)	0.020, 95% CI [0.015; 0.025]
$MPA_{200}Z$ (MDR) (N=9)	0.015, 95% CI [-0.001; 0.031]
Rifafour (HRZE) (DS) (N=58)	0.017, 95% CI [0.013; 0.021]

No statistically significant differences between groups

Of note, ten subjects with MDR-TB remained in the trial for the full 8 weeks of treatment with $MPa_{200}Z$. Nine of these subjects had evaluable logCFU counts that demonstrated a mean daily reduction of 0.117 which compared favorably to the Rifafour group that had a daily reduction of 0.112 over the 56 weeks of therapy. For logTTP the 9 evaluable subjects had daily increases of 0.015 which was similar to the Rifafour group that had daily increases of 0.017.

Table 8: **Summary of Phase 2 Combotherapy 8 Week MPaZ Clinical Trial**

Trial	Design	Trial Treatments (Treatment Duration)	No. Subjects Enrolled and Treated	Key Safety/Efficacy Findings
NC-002	Partially Randomized combination of moxifloxacin plus PA-824 plus pyrazinamide after 8 weeks of treatment in Drug-Sensitive or Multi Drug-Resistant, Smear-Positive Pulmonary Tuberculosis.	DS: • PA-824 200 mg + Z + M • PA-824 100 mg + Z + M • Rifafour e-275 MDR: • PA-824 100 mg + Z + M	• 60 • 62 • 59 • 26	• For the primary endpoint subjects in the $MPA_{200}Z$ arm had a statistically significantly greater decline in the log CFU count over the 8 weeks than the subjects in the HRZE arm. • For the exploratory endpoint all groups had a higher rate of conversion of sputum to a negative culture for *MTB* on solid culture than on liquid culture. Subjects in both of the MPaZ groups had substantially and statistically significantly greater rates of conversion to negative growth in liquid culture than the group on Rifafour (HRZE) • Well tolerated overall, with 88% of all subjects had a treatment emergent adverse event (TEAE), including 87% in the $MPA_{100}Z$ group, 92% in the $MPA_{200}Z$ group, 85% in the Rifafour group and 89% in the MPAZ MDR group • Eleven SAEs were reported in 9 subjects, with one subject in each of the M-PA100-Z and the Rifafour groups, and 7 subjects in the M-PA200-Z group. The subject in the M-PA100-Z group died of an unknown cause 39 days after a single dose of trial drug regimen and the death was not considered related to trial drug by the investigator or the sponsor. Four other SAEs were considered not related to trial drug, including a pneumothorax, a bone fracture, dyspnea requiring hospitalization, and second degree heart block SAEs considered possibly related or related to the trial drug regimen included hyperuricaemia likely secondary from pyrazinamide, drug-induced hepatitis and elevated liver enzymes. One subject had an episode of agranulocytosis that resolved after the trial drug regimen was stopped and one subject had a seizure and was discontinued from the trial.

2.4. Phase 1 and 2 Clinical Safety Results Single Drug and in Combination

2.4.1.PA-824

Across the 15 clinical studies with PA-824 completed to date, a total of 649 subjects have been exposed to PA-824, including 289 healthy subjects across the 10 Phase 1 studies and 360 subjects with newly diagnosed smear positive pulmonary TB across 5 Phase 2 studies. Among the 289 healthy subjects, 174 received exposure to a single dose of PA-824 ranging from 50 to 1500 mg and 115 received exposures to repeated daily doses of PA-824 (50 to 1000 mg) for up to 14 days. The 360 subjects with newly diagnosed smear positive pulmonary TB were exposed to PA-824 either as a single agent at daily doses of 50 to 1200 mg for 14 days or in combination with other anti-TB agents (bedaquiline, moxifloxacin pyrazinamide and/or clofazimine) at a dose of 100 mg or 200 mg for up to 56 days.

Safety has been fully evaluated and reported for the 13 completed trials with final study reports. The safety evaluation is preliminary for the recently completed Phase 2b 8-week NC-002-(M-Pa-Z) trial

Electrocardiographic Thorough QT Trial in Healthy Subjects

The US National Institutes of Health (NIH) sponsored a recently completed Thorough QT trial in 74 healthy volunteers to evaluate the ECG effects of single doses of 400 mg or 1000 mg PA-824 alone, or in combination with moxifloxacin. Assay sensitivity was established for this trial. For moxifloxacin, the lower limit of the 90% confidence interval associated with the least-squares mean ΔΔQTcI value averaged across the 1- to 4-hour postdose timeframe exceeded the 5 ms threshold. PA-824 doses of 400 mg and 1000 mg did not cause QT interval prolongation to a level of clinical concern, as the upper limit of the 90% confidence interval associated with any least-squares mean ΔΔQTcI value did not exceed 4.4 ms for the 400-mg dose or 6.1 ms for the 1000-mg dose, and both were well below 10 ms. The effect of PA 824 400 mg plus moxifloxacin 400 mg on QTcI was similar to the effect of moxifloxacin administered alone. The results of the secondary analyses based on QTcN, QTcF, and QTcB were similar to the results of the primary analysis based on QTcI. The slope of the relationship between QTcI and PA-824 concentration was positive, small in magnitude (0.431 ms/µg/mL), and not statistically significant (p=0.1281).

Safety in Completed Trials of Dosing up to 2 Weeks Duration

The overall safety profile from the completed clinical trials in healthy subjects and TB patients through 2 weeks of dosing indicated that orally-administered PA-824 was well tolerated when administered alone or as a part of a multi-drug anti-TB regimen. In the Phase 2 studies, PA-824-CL-007, PA-824-CL-010 and NC-001-(J-M-Pa-Z), the overall frequency of treatment-emergent adverse events (TEAEs) during the 2-week treatment period was similar for the PA-824 treatment groups and for the standard first-line treatment for TB, Rifafour® e-275. In these Phase 2 studies, the overall frequency of TEAEs with PA-824 did not appear dose related when given at doses ranging from 50 to 200 mg/day in Trial PA-824-CL-010 or from 200 to 1200 mg/day in Trial PA-824-CL-007. In Trial NC-001-(J-M-Pa-Z), the three-drug regimen of moxifloxacin + PA-824 + pyrazinamide was associated with a slightly higher frequency of reported treatment-emergent adverse events (TEAEs) (53%) than were the two-drug regimens of PA-824 + pyrazinamide (47%) or PA-824 + TMC207 (60%).

Reported TEAEs across the 330 subjects exposed to PA-824 in completed clinical trials thus far have generally been mild in intensity, with only about 3% of subjects (one healthy volunteer, nine subjects with pulmonary TB) having a TEAE that was assessed as severe. Almost all TEAEs resolved without sequelae. Five of the 330 subjects (all with pulmonary TB) exposed to PA-824 in the completed studies had a TEAE that met the criteria for being considered serious (pneumothorax, pneumonia, worsening pulmonary TB, hemoptysis, and neurocysticercosis). Each of the serious adverse events (SAEs) reported thus far in subjects exposed to PA-824 were assessed as unrelated to trial treatment, and for two of these subjects, the SAE occurred more than 30 days after the last dose of PA-824.

TEAEs led to discontinuation from trial treatment and/or from the trial for 10 of the 330 subjects exposed to PA-824 (one healthy subject; nine subjects with pulmonary TB). Five of the nine subjects with pulmonary TB who were discontinued due to a TEAE were receiving PA-824 as part of a multi-drug regimen (three were on moxifloxacin + PA-824 + pyrazinamide). For five subjects, the TEAE leading to discontinuation was detected upon laboratory evaluations (alanine aminotransferase [ALT] increased in three subjects; ECG abnormalities [QTc prolonged; Wolff-Parkinson-White syndrome]) and the subjects were asymptomatic. Of the remaining five TEAEs leading to discontinuation, four were assessed as unrelated to trial treatment (SAEs of hemoptysis, pneumothorax, neurocysticercosis; urinary tract infection [subject discontinued to take protocol-disallowed medication]). The remaining TEAE leading to discontinuation was a generalized rash in a healthy subject that presented approximately 32 hours after the final PA-824 dose (1000 mg/day).

In Phase 1 trials, headache was the most common TEAE. Among the 42 subjects across these trials who received a PA-824 dose of 200 mg (anticipated maximum clinical dose) or less, 10 (24%) reported headache. The incidence of headache in subjects treated with placebo in Phase 1 trials PA-824-CL-001 and PA-824-CL-002 was 31% and 22%, respectively. In the Phase 2 studies in subjects with pulmonary TB, in studies PA-824-CL-007 and

PA-824-CL-010, headache was reported for three of the 122 subjects exposed to PA-824 as a single agent in. In Trial NC-001-(J-M-Pa-Z) seven of the 45 subjects exposed to PA-824 as part of a multi-drug regimen in reported headache.

Gastrointestinal disorder TEAEs (primarily nausea and vomiting) and skin and subcutaneous tissue disorder TEAEs (mainly rash) were the most frequently-reported TEAEs in the Phase 2 trials. Gastrointestinal disorder TEAEs were reported for 13 of the 122 subjects (11%) treated with PA-824 across Trials PA-824-CL-007 and PA-824-CL-010 and for four of the 45 subjects (16%) treated with a PA-824-containing regimen in Trial NC-001-(J-M-Pa-Z). None of these TEAEs were severe or serious, or resulted in discontinuation. Skin and subcutaneous tissue disorder TEAEs were reported for 18 of the 122 subjects (15%) across Trials PA-824-CL-007 and PA-824-CL-010, and for three of the 45 subjects (7%) treated with PA-824 in Trial NC-001-(J-M-Pa-Z). Although treatment with PA-824 did appear to be associated with skin-related TEAEs, such as pruritus or rash, these events tended to be mild in intensity and generally resolved without sequelae. Across the 11 clinical trials with PA-824 completed to date (including 8 Phase I studies), only one skin-related TEAE (generalized rash) was severe and resulted in discontinuation from the trial. None were serious.

No other clinically significant changes in laboratory parameters (hematology, clinical chemistry, and urinalysis) have been noted with PA-824 in the Phase 1 or 2 clinical trials. As indicated above, three of the 45 subjects (7%) exposed to a PA-824-containing regimen in Trial NC-001-(J-M-Pa-Z) were withdrawn from treatment due to an elevation in ALT levels. The rate of discontinuation for this laboratory TEAE in this trial was similar to that for bedaquiline-containing regimens (2/30, 7%). Moreover, none of the three subjects discontinued for increased ALT levels in Trial NC-001-(J-M-Pa-Z) had associated symptoms, and in all cases, ALT levels resolved upon discontinuation of treatment. No other hepatic-related TEAEs have been reported in clinical studies with PA-824, and evaluation of hepatic laboratory parameters (ALT, aspartate aminotransferase [AST], total bilirubin) did not suggest any clinically significant changes in these parameters with PA-824.

The initial 3-month nonclinical toxicology trials in rats and monkeys reported the development of cataracts during both treatment and recovery in rats dosed with PA-824 300 mg/kg/day and during the 3-month recovery period in monkeys in the PA-824 450/300-mg/kg/day group. As a result, the Investigational New Drug (IND) application for PA-824 was placed on full clinical hold by the Food and Drug Administration (FDA) in a letter dated 09 April 2008 until additional nonclinical and clinical data were provided. Following submission of nonclinical data from two repeat toxicology trials in rat and monkey, cross-species metabolism comparisons, clinical information on ophthalmologic evaluations in subjects who had participated in multi-dose clinical trials PA-824-CL-005 and PA-824-CL-007, and expert opinions from an independent Ophthalmology Review Board (ORB), the clinical hold was lifted in July 2009. In addition, the FDA requested planned ophthalmologic examinations in future clinical trials. Since the clinical hold was lifted, four additional clinical trials have been conducted, each of which included prospectively-planned ophthalmologic evaluations (slit-lamp examinations, visual acuity testing) predose and at 3- or 6-months after the final dose of trial treatment (Trials PA-824-CL-010, PA-824-CL-006, PA-824-CL-009, NC-001-(J-M-Pa-Z) and NC-002-(M-Pa-Z). Mild lenticular opacities were noted upon ophthalmological slit lamp testing in 2 of the 152 subjects exposed to PA-824 across these five trials; both subjects were asymptomatic.

Rat toxicology trials demonstrated testicular toxicity although there was no evidence of testicular toxicity in mature male monkeys evaluated with PA-824 dosing over 3 months. To gather more information in male subjects regarding male reproductive hormones, serum testosterone, LH and FSH were measured in all male subjects in Trial NC-002-(M-Pa-Z) at baseline and at the end of 8 weeks of exposure to PA-824 and the control HRZE therapy.

<u>Preliminary Safety from Completed Phase 2b 8-Week Trial NC-002-(M-Pa-Z)</u>

Preliminary data analyses of the trial indicate that a total of 207 subjects were enrolled, with 60 randomized to $MPa_{100}Z$, 62 randomized to $MPa_{200}Z$, and 59 to HRZE. An additional 26 subjects were treated in the $MPa_{200}Z$

MDR arm. In this trial 88% of all subjects had a TEAE, including 87% in the $MPA_{100}Z$ group, 92% in the $MPa_{200}Z$ group, 85% in the HRZE group and 89% in the $MPa_{200}Z$ MDR group. Adverse events were graded according to the NIH Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table. Table 9 indicates that TEAEs by grade were comparable by grade across the arms of the trial.

Table 9: **NC-002-(M-Pa-Z) Adverse Events by DMID Grade**

Severity	Statistic	$MPa_{100}Z$ (N=60)	$MPa_{200}Z$ (N=62)	Rifafour (HRZE) (N=59)	$MPa_{200}Z$ MDR (N=26)	Total (N=207)
Grade 1	N (%)	43 (71.7%)	48 (77.4%)	46 (78.0%)	18 (69.2%)	155 (74.9%)
Grade 2	N (%)	25 (41.7%)	31 (50.0%)	27 (45.8%)	13 (50.0%)	96 (46.4%)
Grade 3	N (%)	18 (30.0%)	20 (32.3%)	15 (25.4%)	6 (23.1%)	59 (28.5%)
Grade 4	N (%)	3 (5.0%)	9 (14.5%)	6 (10.2%)	2 (7.7%)	20 (9.7%)

Eleven serious adverse events (SAEs) were reported in 9 subjects, with one subject in each of the $MPa_{100}Z$ and the RHZE groups, and 7 subjects in the $MPa_{200}Z$ group. The subject in the $MPa_{100}Z$ group died of an unknown cause 39 days after a single dose of trial drug regimen and the death was not considered related to the trial drug by the investigator or the sponsor. Four other SAEs were considered not related to trial drug, including a pneumothorax, a bone fracture, dyspnea requiring hospitalization, and second degree heart block considered on evaluation to be existing prior to entry in to the trial. SAEs considered possibly related or related to the trial drug regimen included hyperuricaemia likely secondary from pyrazinamide, drug-induced hepatitis and elevated liver enzymes. One subject had an episode of agranulocytosis that resolved after the trial drug regimen was stopped and one subject had a seizure witnessed by the family and was discontinued from the trial.

The protocol required that subjects with hepatic enzyme ALT or AST elevations greater than 3X the Upper limit of Normal (ULN) must have trial drug discontinued. Consequently, 25 subjects were withdrawn from the trial across the treatment arms for elevations in hepatic enzymes, the distribution across the treatment arms is presented in

Table 10. While more subjects in the MPa_{200}-Z group had elevations in ALT >3 – 5X ULN, those with elevations >5X ULN or >8X ULN were fairly evenly distributed across the groups of subjects with DS-TB.

Table 10: **NC-002-(M-Pa-Z) Elevations in Alanine Aminotransferase**

ALT	Statistic	$MPa_{100}Z$ (N=60)	$MPa_{200}Z$ (N=62)	Rifafour (HRZE) (N=59)	$MPa_{200}Z$ MDR (N=26)
> 3X ULN	N (%)	7	10	5	3
> 5X ULN	N (%)	4	5	4	2
> 8X ULN	N (%)	2	4	3	1

Note: Groups are not mutually exclusive: >3X includes >5X and >8X; >5X includes >8X

Additional safety findings of special focus are noted below.

Ophthalmologic Evaluations – All subjects received ophthalmologic evaluations including visual acuity testing and slit lamp examinations at baseline and 3 months after completion of trial drug dosing. The ophthalmologists were trained in grading 3 regions of the lens using the AREDS2 grading system across a range of 0-4. All subjects enrolled with the required zero score grade for all regions of the lens except for 1 subject who was blind in one eye. Among all subjects in the trial, 4 subjects had lens evaluations with a grade of greater than zero. One subject in the $MPa_{100}Z$ group and 3 subjects in the $MPa_{200}Z$ group had grades of 0.5 or 1.0 in a single eye in one of the 3 zones of the lens. It is unlikely these findings represent a drug-induced lens opacity given the low incidence, the unilateral nature of all findings and the differing zone locations of the findings. It is common in persons with no clinical abnormalities to have grades of 0.5 – 1.0+ in the AREDS2 rating on a slit lamp evaluation.

Reproductive Hormone Evaluations – Preclinical toxicology trials noted that rats dosed with PA-824 developed testicular toxicity, although a 3 month trial in mature monkeys did not identify any drug related testicular toxicity. In Trial NC-002-(M-Pa-Z) men were evaluated with plasma samples for the reproductive hormones LH, FSH and Testosterone at baseline and at the end of the dosing period. If the trial drug regimen caused testicular toxicity, the most sensitive measure from these hormones would be an increase in levels of FSH. Among subjects in the $MPa_{100}Z$ group the mean baseline FSH was 9.027 U/L which decreased to 8.338 U/L at the end of therapy. Among subjects in the $MPa_{200}Z$ group the mean baseline FSH was 6.531 U/L at baseline and this decreased to a mean of 6.061 at the end of therapy. Men in the Rifafour/HRZE group had a mean baseline of 7.394 U/L which decreased to 6.714 at the end of therapy. This gives relative reassurance that the MPaZ regimen is not likely to cause testicular toxicity in men.

Electrocardiographic Conduction Interval Changes – Subjects in NC-002-(M-Pa-Z) had supine resting ECGs taken at baseline, Day 4 and weekly through the 8 week dosing period and 2 weeks after the end of dosing. All ECGs were read by a central cardiology service. No subjects had a corrected QT interval (QTcF) greater than 500 msec during the trial. A small number of subjects had asymptomatic increases in QTcF from baseline over 60 msec: Two in the $MPa_{100}Z$ group, 4 in the $MPa_{200}Z$ group, none in the Rifafour (HRZE) group and 2 in the $MPa_{200}Z$ MDR group. An evaluation of the mean change from baseline across all post-baseline ECGs notes increases of 11.1 msec in the Rifafour (HRZE) group, 11.1 in the $MPa_{100}Z$ group, 17.8 msec in the $MPa_{200}Z$ group and 6.7 in the $MPa_{200}Z$ MDR group. Of note, many subjects were tachycardic at baseline with their active pulmonary TB and had heart rates decrease over the first week of therapy. This fact complicates interpretation of the data based on the QT correction factors that are imperfect when correcting for heart rates that change over time.

2.4.2.Moxifloxacin

In Trial 27 [20], the moxifloxacin-containing TB regimens (HRZM) were shown to be safe and well tolerated. There was no difference in SAEs between the HRZM and HRZE treatment arms, and most SAEs were hospitalizations thought to be unrelated to the trial treatment. Subjects treated with moxifloxacin-containing regimen were more likely to report nausea (22% vs. 9%, p = 0.002), but this was generally mild and did not lead to treatment discontinuation as similar proportions of subjects in both groups completed trial drug treatment (88% HRZM-treated vs. 89% HRZE-treated). The one death during the first 2 months of treatment was thought to be caused by pulmonary embolism, unrelated to tuberculosis therapy.

In the OFLOTUB trial [14], AEs and SAEs occurred with equal frequency in the four treatment arms. The most frequent AEs were raised amylase (in 41% of subjects due to HIV infection), raised transaminase (10%), arthralgia (9%), anemia (7%), hypokalaemia (6%) and vomiting (5%). No subject was withdrawn from the trial due to an adverse event. There were 4 deaths in the trial: 2 in the control group, 1 each in the moxifloxacin and ofloxacin arms. Importantly, subjects in this trial who received moxifloxacin and pyrazinamide in addition to isoniazid and rifampin had more rapid sputum clearance than subjects on the four standard first line drugs (isoniazid, rifampin, pyrazinamide and ethambutol). This difference was evident 14 days after initiation of treatment.

In the JHU trial [19], AEs did not differ by treatment group. There were 16 SAEs (8 in each group) in 12 subjects. Only 1 event was judged related to trial drug (grade 3 cutaneous reaction in the ethambutol group). Eight subjects died during the trial, including 1 in each group still receiving trial phase treatment. No death was attributed to trial treatment. Only 5 subjects discontinued treatment because of toxic effects; 2 subjects in the moxifloxacin group stopped because of grade 2 nausea and vomiting and 1 because of grade 2 paraesthesias and ataxia. Two subjects in the ethambutol group stopped because of grade 2 rash and pruritis and 1 because of grade 3 peripheral neuropathy. There was no change in the QTc interval on serial electrocardiograms taken during the trial.

In Trial 28[21], the proportions of subjects with SAEs during intensive phase treatment were similar between arms (isoniazid 3.9% vs. moxifloxacin 4.2%; P = 0.88). Three SAEs attributed to trial treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group. Seven subjects died during the trial including 3 subjects receiving the moxifloxacin treatment regimen and 4 subjects receiving the isoniazid treatment regimen. All 3 moxifloxacin subjects died during intensive phase TB treatment. Two subjects died from advanced pulmonary TB judged not related to trial treatment and 1 subject (who developed diabetic ketoacidosis considered possibly related to trial treatment) died from possible acute pulmonary embolus unrelated to trial treatment. The 4 isoniazid deaths occurred during continuation phase, and all 4 were considered unrelated to trial treatment. Nausea was more common among subjects in the moxifloxacin arm than in the isoniazid arm (19.6% vs. 11.7%, respectively; P = 0.03) although similar proportions reported vomiting. However, the proportions of subjects with hepatitis, defined as serum aspartate aminotransferase (AST) 3 times or greater than the upper limit of normal, were similar between treatment arms during intensive phase (isoniazid 3.4% vs. moxifloxacin 3.3%; P = 0.93).

Refer to section 2.4.1 for the Preliminary Safety from Completed Phase 2b 8-Week Trial NC-002-(M-Pa-Z).

2.4.3.Pyrazinamide

The pyrazinamide product label notes that Pyrazinamide is contraindicated in persons with severe hepatic damage, who have shown hypersensitivity to it, and with acute gout. The most serious side effect is hepatotoxicity. Its frequency appears to be dose- related and thus liver function should be assessed before and regularly during treatment with pyrazinamide. Hyperuricemia commonly occurs and is occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anemia and dysuria.

Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert [12].

Refer to section 2.4.1 for the Preliminary Safety from Completed Phase 2b 8-Week Trial NC-002-(M-Pa-Z).

2.5. Known and Potential Risks and Benefits of the Investigational Medicinal Product/s

2.5.1.PA-824

The most common side effects or AEs associated with PA-824 exposure include:

- Headache
- Benign, isolated and reversible elevations of serum creatinine
- Stomach discomfort (nausea, vomiting, flatulence, and/or diarrhea)
- Skin and subcutaneous tissue disorders

For additional information refer to PA-824 IB [7].

2.5.2.Moxifloxacin

In the usual daily doses of 400 mg/day, moxifloxacin is well tolerated. As stated in the Package Insert [11] the most frequent individual drug related AEs observed in clinical trials with 400 mg oral moxifloxacin therapy were nausea (7.5%) and diarrhea (5.8%). Fluoroquinolones, including moxifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. A known but rare side effect of fluoroquinolones, including moxifloxacin is exacerbation of myasthenia gravis. In addition, moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some subjects. It should be used with caution in subjects being treated concomitantly with other drugs where an additive effect on the QT interval cannot be excluded. Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, may occur after the first or subsequent doses of moxifloxacin. Also, moxifloxacin may cause peripheral neuropathy. For additional information, refer to the moxifloxacin package insert [11].

2.5.3.Pyrazinamide

The dose of pyrazinamide that will be used in this trial is an approved dosage for the treatment of TB. The most serious side-effect of pyrazinamide is hepatotoxicity and its frequency appears to be dose-related. Hyperuricemia commonly occurs, occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side-effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anemia and dysuria. Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medications may be necessary. For additional information on pyrazinamide, refer to the manufacturer's package insert [12].

2.5.4.RHZE Control

Subjects in the standard treatment arm will receive intensive phase pulmonary TB treatment, which is RHZE 150/75/400/275 mg oral daily (R=rifampicin: H=isoniazid: Z=pyrazinamide: E=ethambutol) for 8 weeks followed by 8 weeks RHZE 150/75 mg oral daily.

Please see the HRZE and HR Package Inserts [22, 23] for known and potential risks and benefits.

3. TRIAL RATIONALE AND OBJECTIVES

3.1. Rationale

3.1.1.Trial Rationale

PA-824, a new chemical entity with significant promise for shortening treatment of active TB, has been under development for several years, and entered clinical trials in 2005. This trial will be the fifth trial of this compound in drug sensitive TB and the second in MDR subjects. As described above, several trials of PA-824 have also been conducted previously in healthy volunteers. Collectively, these trials in subjects with active TB and healthy subjects have defined the efficacy, safety and pharmacokinetic features of the drug. Overall, PA-824 has mycobactericidal activity in subjects and is well tolerated and bioavailable after oral dosing. Moxifloxacin is an approved drug for several indications and while not approved for TB by most regulatory authorities, it is regularly used in second line MDR-TB treatment. The WHO TB Treatment Guidelines place moxifloxicin in the category of Group 3 drugs and notes that "all patients [with MDR-TB] should receive a Group 3 medication if the M. tuberculosis strain is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice." [24]. It is currently in late stage clinical development for first-line TB treatment in combination with other TB drugs, including pyrazinamide in two different four-month long regimens. Pyrazinamide is an approved anti-tuberculosis agent which is indicated for the initial treatment of active tuberculosis in adults and children when combined with other antituberculosis agents and contributes significantly to the sterilization of lesions and thus treatment shortening.

As previously stated, data from preclinical trials suggest that a regimen consisting of moxifloxacin plus PA-824 plus pyrazinamide may not only be appropriate for treating both DS and MDR-TB but may also shorten duration of therapy. Results from an eight week Phase 2b SSCC trial, NC-002-(M-Pa-Z), showed that this combination regimen was effective as measured by time dependent decline of viable bacteria in subjects with DS pulmonary TB. The combination was also shown to be safe and well tolerated supporting the evaluation of this combination in a Phase 3 trial. In this trial 71.4% of subjects with DS-TB treated with PaMZ at the 100 mg daily dose of PA-824 converted sputum to negative for *MTB* growth in liquid culture in comparison with only 37.8 % of subjects treated with the HRZE control ($p<0.05$).

Trials in mice infected with *MTB* demonstrated reductions in cultured colony counts from lungs over an 8 week period when treated with the PaMZ regimen that were substantially, and statistically significantly greater, than the reductions in mice treated with an HRZ control. Experiments in mice found that mice did not relapse with *MTB* infection when treated with PaMZ for 4 months and followed for 3 months off treatment, in comparison to mice that required 6 months of treatment with HRZ to prevent relapse [(14)].

Therefore the purpose of the present trial is to assess the efficacy, safety and tolerability of the combination after 4 and 6 months of treatment in adult subjects with drug sensitive TB and after 6 months of treatment in subjects with multi drug-resistant TB.

3.1.2. Dose Rationale

The dose of **PA-824** in this trial is based on data from two dose-ranging EBA trials that evaluated 14 daily doses ranging from 50 mg to 1200 mg in subjects with pulmonary TB, from the 14 day EBA trial NC-001-(J-M-Pa-Z) and also from the Phase 2 8 week (NC-002-(M-Pa-Z)) bactericidal activity trial. In the monotherapy EBA trials a daily dose of 50 mg had lower bactericidal activity the higher doses. There was no clear difference in bactericidal activity of daily doses ranging from 100 mg to 1200 mg. The Phase 2 EBA regimen trial NC-001-(J-M-Pa-Z) demonstrated good bactericidal activity in the MPaZ combination at a daily dose of 200 mg. The Phase 2 trial NC-002-(M-Pa-Z) evaluated this regimen at doses of PA-824 of both 100 mg and 200 mg relative to the HRZE control. In this trial the efficacy results were similar between subjects treated with 100 mg/day and 200 mg/day of PA-824 in the regimen, although for the primary endpoint, reduction in colony forming units of *MTB* from sputum, only the 200 mg/day dose group was statistically significantly better than the 100 mg/day group. Safety was also similar between the groups, although the 200 mg/day group had more grade 2 adverse events than either the 100 mg/day group or the HRZE control group. Consequently, the PaMZ regimen will be evaluated in one group of subjects with DS TB treated with 100 mg/day for 4 months and in another group treated with 200 mg/day for 4 months. A third group with DS TB will be treated with 200 mg/day for 6 months in the same way as the subjects with MDR-TB will be treated.

Moxifloxacin will be dosed at standard registered daily doses of 400 mg/day.

Pyrazinamide is currently dosed in the marketplace according to weight, although specific weight bands and the number of weight bands vary by country. Mixing weight-banded and non-weight-banded drugs in the same marketed TB treatment regimen, if the drugs are co-packaged or made into fixed dose combination tablets, would pose significant challenges for distribution channels in the developing world because the number of presentations required would be large. This trial aims to evaluate three drugs all given at a fixed dose level so a fixed dose combination tablet may be developed for more acceptable and compliant use in the market. TB Alliance therefore worked with colleagues at Glaxo SmithKline to determine whether weight banding of pyrazinamide in a new regimen is expected to be necessary, either for safety or efficacy reasons, and determined that it is not [(25)]. Targeting the 25th to 90th percentiles of exposure (AUC) in subjects dosed in 3 key weight bands, various fixed doses of pyrazinamide were investigated in this model and the fixed dose of 1500 mg was chosen as optimal for producing exposure in this range for the TB subject population. In addition, the literature on hepatotoxicity of pyrazinamide was reviewed. The incidence of hepatotoxicity was found to be only partially explained by exposure (or dose), but, to be conservative in the modeling, hepatotoxicity was assumed

to be entirely related to exposure. Even with this assumption, it was found that a fixed 1500 mg dose of pyrazinamide is expected to approximately double the number of subjects above the 90th percentile of exposure when dosed using 3 weight bands, but the incidence of hepatotoxicity is predicted to rise only by <1%. From these analyses it was concluded that pyrazinamide can safely and reasonably be tested in clinical trials at a fixed 1500 mg dose. The fixed 1500 mg dose was used in the M-Pa-Z regimen given in the 8 week NC-002-(M-Pa-Z) trial. In that trial subjects received the 1500 mg fixed dose of pyrazinamide in the regimen; it was well tolerated and elevations in hepatic enzyme levels were similar to that in the cohort that received the control HRZE regimen that administered pyrazinamide according to conventional weight bands.

3.1.3.Rationale for Open-Label

This is an open-label trial. The trial subjects, the site staff, sponsor and CROs will not be blinded to treatment assignment. However, it is planned that the applicable sponsor staff (such as medical monitors, trial statisticians (DSMC statisticians will be un-blinded), project managers, central radiologists, co-ordinating investigator), and bacteriology laboratory personnel will be blinded to treatment assignment, unless they need to know the treatment assignment in order to make decisions which effect the subjects safety or adverse event reporting requirements. The key reasons for conducting this trial open-label are:

- Rifampicin predictably causes orange-red discoloration of urine and other bodily fluids, and thus subjects in the control arm will be functionally un-blinded to themselves and to the site. As the trial drug regimen does not contain rifampicin, this cannot be masked.
- The control regimen and investigational regimen are administered under different conditions relative to meals, which makes it unfeasible to double-blind the Investigational Medicinal Product (IMP).
- Burdensome number of tablets/ capsules. Because of the required weight banding for the control regimen, in order for the trial to be fully blinded and placebo- controlled, subjects would need to be administered 10 tablets daily for the first 2 months of the trial.
- Additional considerations are the logistics involved in the different treatment durations in the experimental arms which would require multiple packaging configurations in the last 2 months of the trial.

The following have been considered in order to minimise bias:

- The primary endpoint is based on objective microbiology. The bacteriology laboratory staff will be blinded to the subject's treatment.
- The endpoints of bacteriologic failure or relapse or death are precisely and objectively defined and are not based on subjective assessments.
- Safety assessments will be defined as objectively as possible, such as the definitions of Serious Adverse Events, pre-defined grading criteria for laboratory abnormalities, and adverse events.

3.1.4.Rationale for Inclusion of Subjects with MDR-TB without a MDR Control Group

The current standard of care for subjects with MDR-TB according to WHO Guidelines recommends an intensive phase of treatment with 5 drugs, including a parenteral drug, for 8 months and a continuing phase for a total duration of 20 months for subjects not previously treated for MDR-TB [(26)]. Subjects with MDR-TB previously treated may require up to 30 months or longer of treatment. The complexity, length and toxicities of the currently available regimens for MDR-TB are a challenge to include in a trial of a shorter novel regimen. The efficacy of the Bangladesh regimen has previously been demonstrated [(27)]. This is a 7 drug combination, 9 month regimen for MDR-TB which consists of high-dose H, gatifloxacin, kanamycin, prothionamide, ethambutol, Z and clofazimine given for 9 months.

Because the MPaZ regimen in this trial does not include either H or R it is expected that the regimen will have effective bactericidal activity in subjects with MDR-TB but who have TB organisms that are susceptible to Z and M. These drugs, and PA-824, have low MICs and significant activity in vitro against multiple MDR-TB strains, and in Trial NC-002-(M-Pa-Z) subjects with MDR-TB had substantial reductions in CFU counts over 2-8 weeks similar

to the subjects with DS-TB. This trial is designed to demonstrate that the trial regimen administered over 6 months to subjects with MDR-TB has comparable efficacy per the primary endpoint as the regimen administered to subjects with DS-TB. No formal statistical comparison will be made for the group with MDR-TB. The demonstration of comparable efficacy to the subjects with DS-TB administered the investigational regimen is analogous to evaluating the efficacy of subsets of a population in a trial, such as men vs women, racial subgroups or sites by region. Such a finding will demonstrate that the regimen has substantial benefit compared to the regimens currently recommended for treating MDR-TB.

3.1.5. Rationale for Follow up Time Periods

Subjects will be followed up for 24 months after start of treatment. After the final subjects have been followed up for a minimum of 12 months from start of treatment, an interim database lock and analysis will occur and the initial file for regulatory approval for marketing authorization made per this analysis. After all subjects have been followed for 24 months after start of treatment there will be a second database lock and data analysis. Depending on the MDR-TB recruitment rate enrolment into this arm may be continued after enrolment into the DS-TB arms is complete and a third database lock may be required for this data. An analysis of 15 tuberculosis treatment trials determined that 78% of all relapses occurred within 6 months of stopping treatment and 91% occurred within 12 months [(28)]. Thus, the initial data base lock and interim analysis will occur when all subjects have been followed a minimum of 6 months after their last dose of trial drug and many will have been followed for substantially longer. This follow up will allow the determination of non-inferiority of the investigational regimen relative to the standard control regimen at a time when the majority of any relapses will have occurred.

3.1.6. Rationale for a Non-Inferiority Design

The current standard regimen for treating TB is 2 months of “intensive phase” treatment with H+Z+E+R followed by 4 months of “continuation phase” treatment with H+R (the standard “HRZE/HR” regimen). These drugs were all approved decades ago. Success rates in early clinical trials using the standard HRZE regimen were very high (>95%), making a non-inferiority comparison to current therapy the only viable clinical trial design, given that a placebo control group cannot be justified. A significant consideration is the fact that more recent clinical trials have resulted in treatment failure and relapse rates using the standard HRZE therapy that are substantially higher than the historic rates that are often used to calculate power and establish non-inferior (NI) Margins in clinical trials. For example, a recently published trial found the success rate of standard HRZE therapy to be approximately 84% at 18 months after randomization (12 months post-treatment) in the modified intent to treat (MITT) analysis [(29)]. The reasons for the differences observed in treatment success rates between contemporary and historical trials might include: 1) current regulatory requirements (e.g., early deaths can no longer reasonably be excluded from the analyses); 2) the inclusion in contemporary trials of HIV positive patients, not all of whom are adequately treated for their underlying HIV disease; 3) the inclusion in contemporary trials of more patients with H monoresistance; and 4) fewer non-protocol treatment options during historical trials, such that patients may have been less likely to be switched prematurely to other therapy.

The current generally accepted primary endpoint for TB clinical trials is based on a microbiological and clinical assessment of outcome: favorable (cure) versus unfavorable (treatment failure or relapse). There is no modern placebo-controlled clinical trial data to use in estimating an appropriate non-inferiority margin for Phase 3 trials.

This trial aims to demonstrate that the experimental regimen administered for either 4 or 6 months to subjects with DS-TB is not inferior to the standard 6 month control regimen using a non-inferiority margin of 12% chosen based on the following rationale. The best estimate for the treatment effect (also known as M1 in guidance documents for non-inferiority trials of the current standard treatment (HRZE) is derived from modern clinical trials of this treatment compared to historical, natural history trials. Based on the above reference an estimate of the favorable rate observed with standard HRZE therapy of 84%, is used. The WHO estimates that the case fatality rate for untreated smear positive pulmonary tuberculosis is 70%, and this estimate was recently confirmed in a systematic review [(30)]; therefore an estimate of 30% for the favorable rate of placebo may be

contrasted with the 84% favorable rate of the standard HRZE therapy. Based on these data, the best available point estimate for M1 (the overall treatment effect of HRZE) is 54%. A conservative selection of 12% for M2 (the non-inferiority margin) would represent less than 25% of the point estimate of M1, thus requiring that the lower bound of the NI margin preserve more than 75% of the estimated treatment effect of the HRZE regimen.

3.2. Trial Objectives

3.2.1. Primary Objectives

Assess the efficacy, safety and tolerability of moxifloxacin 400 mg plus PA-824 100 mg plus pyrazinamide 1500 mg regimen after 4 months of treatment, moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg regimen after 4 months of treatment, moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg regimen after 6 months of treatment in subjects with DS pulmonary TB compared to standard HRZE treatment.

3.2.2. Secondary Objectives

Evaluate whether the efficacy safety and tolerability of the moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg regimen after 6 months of treatment in subjects with MDR pulmonary TB compared to $MPa_{200}Z$ treatment in DS-TB subjects.

3.2.3. Exploratory Objectives

1. Evaluate whether the rate of change in log time of sputum culture positivity log(TTP) over time in liquid culture (MGIT) at early time points predicts relapse-free cure.
2. Evaluate whether time to sputum culture conversion to negative status predicts relapse-free cure.
3. Evaluate whether the proportion of subjects with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 8, 12 and 17 weeks predicts definitive outcome of relapse-free cure.
4. Evaluate separately the subjects with isoniazid monoresistance to determine the consistency of their results with those of the isoniazid sensitive subjects.
5. Evaluate separately the subjects with rifampicin monoresistance to determine the consistency of their results with other subjects considered to have MDR-TB.

4. TRIAL DESIGN

4.1. Summary of Trial Design

This is a Phase 3, multi-center, open-label, partially randomized clinical trial conducted in five parallel treatment groups. The trial will be performed at multiple centers located world-wide.

Prior to randomization, there will be a screening period of up to 9 (DS-TB) or 14 (MDR-TB) days. A total of up to 1,500 (dependent on the number of MDR-TB patients enrolled) male and female subjects, diagnosed with DS or MDR, smear-positive pulmonary TB aged 18 years and over. A total of 1,200 DS-TB subjects (300 per treatment arm) will be randomized. Up to or equal to 300 MDR-TB subjects will be assigned.

Of these 1,500 subjects:

- 1,200 subjects will have DS pulmonary TB and will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups:
  1. Moxifloxacin 400 mg plus PA-824 100 mg plus pyrazinamide 1500 mg daily for 4 months;
  2. Moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg daily for 4 months;
  3. Moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg daily for 6 months;
  4. HRZE (isoniazid (H) 75 mg plus rifampicin (R) 150 mg plus pyrazinamide (Z) 400 mg plus ethambutol (E) 275 mg) combination tablets dosed per weight daily for 2 months followed by HR (isoniazid 75 mg plus rifampicin 150 mg) combination tablets dosed per weight daily for 4 months.

- Up to or equal to 300 subjects will have MDR pulmonary TB and will be assigned to the following treatment group:
  5. Moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg daily for 6 months.

Table 11: Treatment Groups

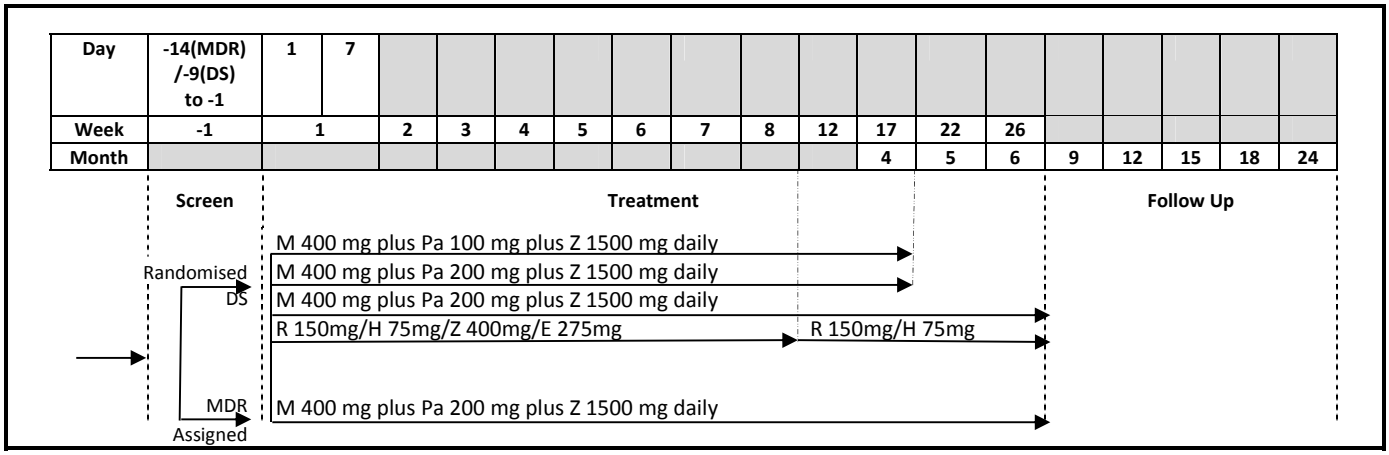
	Treatment Group	Subject Population	Duration of Treatment	No. of Subjects
1.	Moxifloxacin 400 mg + PA-824 100 mg + Pyrazinamide 1500 mg	DS-TB	17 weeks	300
2.	Moxifloxacin 400 mg + PA-824 200 mg + Pyrazinamide 1500 mg	DS-TB	17 weeks	300
3.	Moxifloxacin 400 mg + PA-824 200 mg + Pyrazinamide 1500 mg	DS-TB	26 weeks	300
4.	HRZE combination tablets followed by HR combination tablets.	DS-TB	8 weeks HRZE + 18 weeks HR	300
5.	Moxifloxacin 400 mg + PA-824 200 mg + pyrazinamide 1500 mg	MDR-TB	26 weeks	≤300

The daily dose of HRZE and HR combination tablets are dependent on the subject's weight as follows:

30-39 kg: 2 tablets
40-54 kg: 3 tablets
55-70 kg: 4 tablets
>70 kg: 5 tablets

All subjects will be followed up for a period of 24 months from start of therapy.

Figure 8: Trial Schematic



A separate semen sub-trial will be performed at pre-identified sites also involved in the parent trial. A separate sub-trial protocol will be written to cover all aspects of this sub-trial.

There will be either two/three/four database locks, data analyses and trial reports generated for this trial, depending on the MDR-TB recruitment rate:

1. When all DS-TB subject have completed 12 months follow-up from start of therapy. This will be used for submission for Market Authorization Approval.
2. When all DS-TB subjects have completed 24 months follow-up from start of therapy.
3. When MDR-TB recruitment is closed and subjects have completed 12 and/or 24 month follow up from start of therapy.

4.2. Trial Endpoints

4.2.1. Primary Endpoint

Incidence of bacteriologic failure or relapse or clinical failure at 12 months from the start of therapy.

Abbreviated Definitions (full definitions will be described in the Statistical Analysis Plan (SAP)):

- Bacteriologic failure: During the **treatment period**, failure to **attain** culture conversion to negative status in liquid culture.
- Bacteriologic relapse: During the **follow-up period**, failure to **maintain** culture conversion to negative status in liquid culture, with culture conversion to positive status with a *MTB* strain that is genetically **identical to** the infecting strain at baseline.
- Bacteriologic reinfection: During the **follow-up period**, failure to **maintain** culture conversion to negative status in liquid culture, with culture conversion to positive status with a *MTB* strain that is genetically **different from** the infecting strain at baseline.
- Clinical failure: A change from protocol-specified TB treatment due to treatment failure, retreatment for TB during follow up, or TB-related death.

Note:

- Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.
- Subjects who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit.

4.2.2. Secondary Endpoints

4.2.2.1. Efficacy

- Incidence of bacteriologic failure or relapse or clinical failure at 24 months from the start of therapy as a confirmatory analysis.
- The rate of change in time of sputum culture positivity (TTP) over time in the MGIT system in sputum, represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time to be explored as a potential biomarker of definitive outcome.
- Time to sputum culture conversion to negative status in liquid culture (MGIT) through the treatment period to be explored as a potential biomarker of definitive outcome.
- Proportion of subjects with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 8, 12 and 17 weeks to be explored as a potential biomarker of definitive outcome.
- Change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status.

4.2.2.2. Safety and Tolerability

- Incidence of Treatment Emergent Adverse Events (TEAEs) will be presented by incidence, severity, drug relatedness, and seriousness, leading to early withdrawal and leading to death.
- Quantitative and qualitative clinical safety laboratory measurements, including observed and change from baseline.
- Quantitative and qualitative measurement of ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed and change from baseline, will be presented.
- QT/QTc intervals, including post baseline and change from baseline, will be categorized.
- Descriptive statistics of ophthalmology slit lamp examination data (age related eye disease trial 2 [AREDS2] lens opacity classification and grading). Categorical data for lens opacity will be summarized in a frequency table for the left and right eye, respectively.
- Changes in male reproductive hormones.
- Semen analysis in a subset of male subjects. Endpoints and analysis will be described in a separate sub-trial protocol.

These data will be presented as descriptive analyses, and no inferential tests will be carried out.

4.2.2.3. Pharmacokinetics (PK)

Plasma concentrations from sparse sampling will be used to build a population PK model to evaluate the effects of baseline subject covariates on trial drug pharmacokinetics and associated clinical endpoints. PK samples from the Phase 2 trials with more frequent PK sampling will be used along with the PK samples in this trial to build the model.

4.2.2.4. Pharmacokinetics-Pharmacodynamics (PK-PD):

Population PK models will be developed using the pre-dose (trough) plasma concentrations of each drug in the combination drug regimen. These population PK models will be used to explore trends in the safety and efficacy data from the trial, and will be presented in a separate report to the Clinical Trial Report for this trial.

4.3. Mycobacterial Characterization:

The *MTB* isolates will be characterized as follows:

- Speciation of the infecting organisms by molecular or antigen based test to confirm MTB;
- MIC against moxifloxacin and PA-824;
- Drug Susceptibility Testing for rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide using an indirect susceptibility test in liquid culture;
- Extraction of organismal (*MTB*) DNA for molecular strain typing.

4.4. Trial Population

Semen sub-trial inclusion and exclusion criteria will be described in the separate semen sub-trial protocol.

4.4.1. Inclusion Criteria

Subjects must meet <u>ALL</u> of the following inclusion criteria in order to participate

1. Signed written consent or witnessed oral consent in the case of illiteracy, prior to undertaking any trial-related procedures.
2. Male or female, aged 18 years or over.
3. Body weight (in light clothing and no shoes) ≥ 30 kg.
4. Sputum positive for tubercule bacilli (at least 1+ on the IUATLD/WHO scale (Appendix 1)) on smear microscopy at the trial laboratory.
5. Drug-Sensitive TB treatment arms subjects should be:

a. sensitive to rifampicin by rapid sputum based test (may be sensitive or resistant to isoniazid) AND
b. either newly diagnosed for TB or have a patient history of being untreated for at least 3 years after cure from a previous episode of TB.

If they are entered into the trial due to being sensitive to rifampicin by rapid sputum based test, however on receipt of the rifampicin resistance testing using an indirect susceptibility test in liquid culture this shows they are rifampicin resistant, they will be:

a. Excluded as late exclusions;
b. Possibly replaced as determined by the sponsor.

MDR-TB treatment arm subjects should be resistant to rifampicin by rapid sputum based test (may be sensitive or resistant to isoniazid).

6. A chest x-ray 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. Subject - not heterosexually active or practice sexual abstinence; or
b. Female subject or male subjects 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 subject or female subjects male sexual partner - vasectomised or has had a bilateral orchidectomy minimally three months prior to screening;

Effective birth control methods:

a. Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or
b. Female subject: Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female patient.
c. Male subjects' female sexual partner: Double barrier method or hormone-based contraceptives or an intra-uterine device for the female partner.

and are willing to continue practising birth control methods and are not planning to conceive throughout treatment and for 12 weeks (male subjects) or 1 week (female subjects) after the last dose of trial medication or discontinuation from trial medication in case of premature discontinuation.

(Note: Hormone-based contraception alone may not be reliable when taking IMP; therefore, hormone-based contraceptives alone cannot be used by female subjects to prevent pregnancy).

4.4.2. Exclusion Criteria

Subjects will be excluded from participation if they meet ANY of the following criteria

Medical History

1. Any non TB related condition (including myasthenia gravis) where participation in the trial, as judged by the investigator, could compromise the well-being of the subject or prevent, limit or confound protocol specified assessments.
2. Being or about to be treated for Malaria.
3. 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.
4. TB meningitis or other forms of extrapulmonary tuberculosis with high risk of a poor outcome, or likely to require a longer course of therapy (such as TB of the bone or joint), as judged by the investigator.

5. History of allergy or hypersensitivity to any of the trial IMP or related substances, including known allergy to any fluoroquinolone antibiotic, history of tendinopathy associated with quinolones or suspected hypersensitivity to any rifampicin antibiotics.
6. For HIV infected subjects any of the following:

    a. CD4+ count <100 cells/µL;
    b. Karnofsky score <60% (Appendix 2);
    c. Received intravenous antifungal medication within the last 90 days;
    d. WHO Clinical Stage 4 HIV disease (Appendix 3).

7. Resistant to fluoroquinolones (rapid, sputum – based molecular screening tests).
   If they are entered into the trial due to being sensitive to fluoroquinolones by rapid sputum based test, however on receipt of the fluoroquinolones resistance testing using an indirect susceptibility test in liquid culture this shows they are fluoroquinolones resistant, they will be:

    a. Excluded as late exclusions;
    b. Possibly replaced as determined by the sponsor.

8. Resistant to pyrazinamide (rapid, sputum – based molecular screening tests).
   Drug-Sensitive TB treatment arms subjects may be entered prior to receipt of the rapid, sputum – based molecular pyrazinamide resistance screening test result. On receipt of the result, if they are resistant, they will be:

    a. Excluded as late exclusions;
    b. Possibly replaced as determined by the sponsor.

   MDR-TB treatment arm subjects may **not** be entered prior to receipt of the rapid, sputum – based molecular pyrazinamide resistance screening test result showing they are sensitive to pyrazinamide.

9. Having participated in other clinical trials with investigational agents within 8 weeks prior to trial start or currently enrolled in an investigational trial.
10. Subjects with any of the following at screening (per measurements and reading done by Central ECG where applicable):

    a. Cardiac arrhythmia requiring medication;
    b. Prolongation of QT/QT_c interval with QTcF (Fridericia correction) >450 ms;
    c. History of additional risk factors for Torsade de Pointes, (e.g., heart failure, hypokalemia, family history of Long QT Syndrome);
    d. Any clinically significant ECG abnormality, in the opinion of the investigator.

11. Unstable Diabetes Mellitus which required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening.

<u>Specific Treatments</u>

12. Previous treatment with PA-824 as part of a clinical trial.
13. For DS-TB treatment arms: Previous treatment for tuberculosis within 3 years prior to Day (-9 to -1)(Screening). Subjects who have previously received isoniazid prophylactically may be included in the trial as long as that treatment is/was discontinued at least 7 days prior to randomization into this trial.
    For the MDR-TB Subjects: Previous treatment for MDR-TB, although may have been on a MDR TB treatment regimen for no longer than 7 days at start of screening.
    Previous treatment for TB includes, but is not limited to, gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.
14. Any diseases or conditions in which the use of the standard TB drugs or any of their components is contra-indicated, including but not limited to allergy to any TB drug, their component or to the IMP.

15. Use of any drug within 30 days prior to randomisation known to prolong QTc interval (including, but not limited to, amiodarone, amitriptyline, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinacrine, quinidine, sotalol, sparfloxacin, thioridazine).
16. Use of systemic glucocorticoids within one year of start of screening (inhaled or intranasal glucocorticoids are allowed).
17. Subjects recently started or expected to need to start anti-retroviral therapy (ART) within 1 month after randomization. Subjects may be included who have been on ARTs for greater than 30 days prior to start of screening, or who are expected to start ART greater than 30 days after randomization.

Laboratory Abnormalities

18. Subjects with the following toxicities at screening as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November 2007)(Appendix 4), where applicable:

    a. creatinine grade 2 or greater (>1.5 times upper limit of normal [ULN]);
    b. creatinine clearance (CrCl) level less than 30 mLs/min according to the Cockcroft-Gault Formula (Appendix 5);
    c. haemoglobin grade 4 (<6.5 g/dL);
    d. platelets grade 3 or greater (under $50x10^9$ cells/L/ 50 000/mm^3);
    e. serum potassium less than the lower limit of normal for the laboratory. This may be repeated once;
    f. aspartate aminotransferase (AST) grade 3 or greater (≥3.0 x ULN) ;
    g. alanine aminotransferase (ALT) grade 3 or greater (≥3.0 x ULN);
    h. alkaline phosphatase (ALP):
        - grade 4 (>8.0 x ULN) to be excluded;
        - grade 3 (≥3.0 – 8.0 x ULN) must be discussed with and approved by the sponsor Medical Monitor;
    i. total bilirubin:
        - > 2.0 x ULN, when other liver functions are in the normal range
        - >1.50 x ULN when accompanied by any increase in other liver function tests
            - subjects with total bilirubin > 1.25 x ULN and accompanied by any increase in other liver function tests must be discussed with the sponsor medical monitor before enrollment

All of the inclusion and none of the exclusion criteria must be met. If no single variable/value is outside of the ranges of acceptability, but when multiple values are close to the limits and/or whenever the investigator has reason to suspect that there might be a health problem (other than TB), enrolment should only be considered after discussing the case with the sponsor medical monitor.

4.4.3. Restrictions

Concomitant medications should be kept to a minimum during the trial. However, if concomitant medications are considered to be necessary for the subject'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 a worsening of an existing condition occurring after signing of the informed consent form, the condition must be documented on the Adverse Event pages of the electronic Case Report Form (eCRF).

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

The following recommendations should be followed with regards to concomitant medication to avoid possible drug interaction with the IMP:

- Subjects on a moxifloxacin containing treatment arm: The IMP should be taken either 4 hours before or 8 hours after taking the following products:
  - An antacid, multivitamin, or other product that has magnesium, aluminium, iron or zinc;
  - Sucralfate;
  - Didanosine.
- Subjects on the HRZE/HR treatment arm: Any aluminium-containing antacids should be taken at least one hour after the IMP dose.

The following medicinal products are prohibited from Day -14(MDR)/-9(DS) to Day -1 (Screening) and during the treatment period:

- Quinolone antimalarials (e.g., chloroquine and quinacrine). Subjects who have malaria at screening are to be excluded. However if a subject develops malaria during the course of the trial, the investigator is advised to consult the Malaria Treatment Guidance document (Appendix 6) regarding the interaction between moxifloxacin and anti-malarial drugs. Investigators may also contact the sponsor medical monitor for further guidance.
- Systemic glucocorticoids (inhaled or intranasal glucocorticoids are allowed).
- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.
- Any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). The exception is moxifloxacin administered as part of the trial IMP with ECG monitoring to help ensure subject safety.

4.5. Investigational Plan: Schedule of Assessments

The scheduled dates for trial visits will all be individually calculated from the date of the Day 1 (baseline) visit.

The trial consists of three periods, as follows:

- Screening Period (Day -14(MDR)/-9(DS) to Day -1);
- Treatment Period (Day 1 to Week 26 (Month 6));
- Follow-up Period (Month 6 to Month 24).

Hospitalization is not required for trial participation, however may be considered when necessary per local guidelines (e.g. for MDR-TB if required).

Refer to:

- Trial Flow Chart (Section 1.2) for the timing of all procedures and laboratory samples to done at each visit;
- Trial Procedures (Section 6) for details regarding specific procedures or laboratory tests.

4.5.1.Screening Period (Day (-14(MDR)/-9(DS) to -1))

Screening may occur over a number of days i.e. all screening procedures do not have to be performed on the same day. The Screening time period will be up to a maximum of 9 days for DS-TB subjects and 14 days for MDR-TB subjects. Should a site's ethics committee request that this be modified, the agreed upon time period will be implemented for that site.

The following information will be collected and procedures performed:

1. Written Informed Consent (including HIV) will be obtained prior to all trial related procedures;
2. Demography;

3. Clinically Significant Medical, Treatment and Smoking History;
4. Eligibility Assessment;
5. Two Screening Spot Sputum Sample collection (at the research site under the coaching and observation of the trial staff);
6. HIV test and CD4 count;
7. Karnofsky Score;
8. Serum Pregnancy test (women of child bearing potential, whether they are sexually active or not);
9. Laboratory Safety sampling (including male reproductive hormone tests);
10. Single 12-lead ECG;
11. Chest X-Ray;
12. TB Symptoms Profile (Appendix 7);
13. Patient Reported Health Status Questionnaire (Appendix 8);
14. Vital Signs;
15. Full Physical Examination including weight and height;
16. Ophthalmology Examination.

4.5.2. Treatment Period (Day 1 to Week 26 (Month 6))

Allowed Window Periods: Weeks 1 to 8 ±3days; Weeks 12 – 26 ±7days.

4.5.2.1. Day 1 (Baseline)

Subjects who, following the screening assessments, are eligible for the trial and willing to participate, will be randomised/enrolled into the trial and assigned a Randomization Number.

The following information will be collected and procedures performed prior to dosing:

1. Sputum Sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Serum pregnancy test (women of child bearing potential, whether they are sexually active or not);
3. Laboratory Safety Sampling (including male reproductive hormone tests);
4. Single 12-lead ECG;
5. TB Symptoms Profile;
6. Patient Reported Health Status Questionnaire;
7. Vital Signs;
8. Full Physical Examination including weight;
9. IMP Randomization/Treatment Assignment and Instruction on dosing;
10. Concomitant Medications;
11. Adverse Events.

4.5.2.2. Day 7 (Week 1)

The following information will be collected and procedures performed:

1. Sputum Sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Laboratory Safety sampling (including male reproductive hormone tests);
3. Single 12-lead ECG;
4. Vital Signs;
5. Limited Physical Examination including weight;
6. IMP Compliance Check;
7. Concomitant Medications;
8. Adverse Events.

4.5.2.3. Week 2

The following information will be collected and procedures performed:

1. Sputum Sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Laboratory Safety sampling (including male reproductive hormone tests);
3. Single 12-lead ECG;
4. TB Symptoms Profile;
5. Patient Reported Health Status Questionnaire;
6. Vital Signs;
7. Limited Physical Examination including weight;
8. Pharmacokinetic sampling (pre-dose and after ECGs. Collect time of two doses prior to PK sample collection and the dose following PK sample collection. MPaZ treatment arms only. No PK variables will be collected for the HRZE/HR treatment arm);
9. IMP Compliance Check;
10. Concomitant Medications;
11. Adverse Events.

4.5.2.4. Week 3

The following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Vital Signs;
3. Limited Physical Examination including weight;
4. IMP Compliance Check;
5. Concomitant Medications;
6. Adverse Events.

4.5.2.5. Week 4

The following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Laboratory Safety sampling (including male reproductive hormone tests);
3. TB Symptoms Profile;
4. Patient Reported Health Status Questionnaire;
5. Vital Signs;
6. Limited Physical Examination including weight;
7. IMP Compliance Check;
8. Concomitant Medications;
9. Adverse Events.

4.5.2.6. Weeks 5, 6, 7

The following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Vital Signs;
3. Limited Physical Examination including weight;

4. IMP Compliance Check;
5. Concomitant Medications;
6. Adverse Events.

4.5.2.7. Week 8 (Month 2)

The following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Serum Pregnancy test (women of child bearing potential, whether they are sexually active or not);
3. Laboratory Safety sampling (including male reproductive hormone tests);
4. Single 12-lead ECG;
5. TB Symptoms Profile;
6. Patient Reported Health Status Questionnaire;
7. Vital Signs;
8. Limited Physical Examination including weight;
9. Pharmacokinetic sampling (pre-dose and after ECGs. Collect time of the two doses prior to PK sample collection and the dose following PK sample collection. MPaZ treatment arms only. No PK variables will be collected for the HRZE/HR treatment arm);
10. IMP Compliance Check;
11. Concomitant Medications;
12. Adverse Events.

4.5.2.8. Week 12 (Month 3)

The following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Laboratory Safety sampling (including male reproductive hormone tests);
3. Vital Signs;
4. Limited Physical Examination including weight;
5. IMP Compliance Check;
6. Concomitant Medications;
7. Adverse Events.

4.5.2.9. Week 17 (Month 4)

Subjects who are completing treatment at Week 17 (Month 4), the following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Serum Pregnancy test (women of child bearing potential, whether they are sexually active or not);
3. Laboratory Safety sampling (including male reproductive hormone tests);
4. Single 12-lead ECG;
5. TB Symptoms Profile;
6. Patient Reported Health Status Questionnaire;
7. Vital Signs;
8. Full Physical Examination including weight;
9. IMP Compliance Check;
10. Concomitant Medications;
11. Adverse Events.

Subjects who are continuing treatment to Week 26 (Month 6), the following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Vital Signs;
3. Limited Physical Examination including weight;
4. IMP Compliance Check;
5. Concomitant Medications;
6. Adverse Events.

4.5.2.10. Week 22 (Month 5)

All subjects will have the following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Vital Signs;
3. Limited Physical Examination including weight;
4. Ophthalmology Examination;
5. IMP Compliance Check (subjects on a 6 month treatment arm only);
6. Concomitant Medications;
7. Adverse Events.

4.5.2.11. Weeks 26 (Months 6)

Subjects who have completed treatment at Week 17 (Month 4), the following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Vital Signs;
3. Limited Physical Examination including weight;
4. Concomitant Medications;
5. Adverse Events.

Subjects who are completing treatment at Week 26 (Month 6), the following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Serum Pregnancy test (women of child bearing potential, whether they are sexually active or not);
3. Laboratory Safety sampling (including male reproductive hormone tests);
4. Single 12-lead ECG ;
5. TB Symptoms Profile;
6. Patient Reported Health Status Questionnaire;
7. Vital Signs;
8. Full Physical Examination including weight;
9. IMP Compliance Check;
10. Concomitant Medications;
11. Adverse Events.

4.5.3. Follow-up Period (Month 6 to Month 24)

Allowed Window Periods: Months 9 – 24 ±14days.

4.5.3.1. Month 9

The following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Single 12-lead ECG;
3. Vital Signs;
4. Limited Physical Examination including weight;
5. Ophthalmology Examination;
6. Concomitant Medications;
7. Adverse Events.

4.5.3.2. Month 12

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. TB Symptoms Profile;
3. Patient Reported Health Status Questionnaire;
4. Vital Signs;
5. Limited Physical Examination including weight;
6. Concomitant Medications;
7. Adverse Events.

4.5.3.3. Months 15, 18

The following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Vital Signs;
3. Limited Physical Examination including weight;
4. Concomitant Medications;
5. Adverse Events.

4.5.3.4. Month 24

The following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. TB Symptoms Profile;
3. Patient Reported Health Status Questionnaire;
4. Vital Signs;
5. Limited Physical Examination including weight;
6. Concomitant Medications;
7. Adverse Events.

4.5.4. Early Withdrawal

In case of early withdrawal during the treatment or follow-up period, all efforts shall be made to complete the Early Withdrawal assessments. At the early withdrawal visit the following information will be collected and procedures performed:

1. Sputum sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff);
2. Serum Pregnancy test (women of child bearing potential, whether they are sexually active or not);
3. Laboratory Safety sampling (including male reproductive hormone tests);
4. Single 12-lead ECG;
5. TB Symptoms Profile;
6. Patient Reported Health Status Questionnaire;
7. Vital Signs;
8. Full Physical examination including weight;
9. Ophthalmology Examination if required as described in Table 12;
10. IMP Compliance Check (if subject on IMP);
11. Concomitant Medications;
12. Adverse Events.

Once a subject has been permanently withdrawn from the trial, they will be requested to attend follow-up visits as described in Table 12.

Table 12: Follow-up visits Required for Early Withdrawal Subjects

Treatment Duration at EWD visit	Ophthalmology Examination at EWD	Ophthalmology Examination Visit 3 months after EWD Visit	Month 12 Follow-up Visit	Month 24 Follow-up Visit
≤ 14 days	Not required	Not required	Required	Required
15 days to ≤ 12weeks	Not required	Required	Required	Required
> 12 weeks	Required	Required	Required, if not already performed.	Required

The Month 12 and 24 visits will be to collect SAE information (including verification of survival) and patient reported TB outcome information only and may be telephonic, a home or a site visit. They will occur at Month 12 and/or 24 after the subjects start of treatment date.

If an additional visit is required for a ophthalmology examination after EWD, only the ophthalmology examination will be performed at this visit, and it will occur 3 months after the EWD visit date.

4.5.5. Unscheduled Visits

Any visit which is conducted in addition to those required by the Trial Flow Chart 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 would require a unscheduled visit/s:

- If both sputum samples (Early Morning and Spot) at Month 2 or later are contaminated, the subject should return for an unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the subject is not able to produce sputum.
- If there is a positive culture at or after the end of treatment (Week 17 (4 month treatment arms)/Week 26 (6 month treatment arms)), the subject should return for an unscheduled visit(s) to give additional sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) or to document that the subject is not able to produce sputum.
- In order to be able to define a subject's primary outcome status it may be necessary in certain situations to contact a subject and request they visit the site in order to collect additional sputum samples at Unscheduled Visits, as follows:
    - To be assessed on sputum culture results from:
        - End of Treatment Period (Week 17/26);
        - End of Follow-up Period (Month 12 and 24);
        - Early Withdrawal if applicable.
    - Confirm whether the subject has:
        - two sequential negative sputum culture results; or
        - two sequential positive sputum culture results; or
        - has been unable to produce sputum after documentation of two negative sputum cultures with no intervening positive and are clinically asymptomatic.

    If they **do not** fall into one of these categories, keep collecting Sputum samples x 2 (one early morning and one spot at the research site under the coaching and observation of the trial staff) a minimum of 7 days apart until they fall into one of the above categories.

If in any of the above scenarios the investigator is unsure of the outcome the investigator is to contact the sponsor medical monitor and discuss and agree on how the patient is to be handled.

4.5.6.Treatment Discontinuation and/or Early Withdrawal

Any subject for whom the investigator decides to temporarily discontinue their IMP is to be discussed with the sponsor medical monitor and, if applicable, be restarted on IMP as soon as possible.

A subject must be prematurely withdrawn from the trial (during the trial treatment or follow up periods) as a result of the following:

- Withdrawal of informed consent;
- Investigator considers it for safety reasons in the best interest of the subject that he/she be withdrawn, including a concern that the subject has symptomatic TB and/or bacteriological failure/relapse and requires a change in TB treatment;
- Pregnancy;
- At the specific request of the sponsor or termination of the trial by the sponsor;
- Failure to comply with the protocol;
- Subject misses 21 or more consecutive doses of IMP;
- Drug-Sensitive TB treatment arms subjects, who have been entered prior to receipt of the rapid, sputum – based molecular pyrazinamide resistance screening test result, who on receipt of the result, are found to be Z resistant.
- Drug-Sensitive TB treatment arms subjects, who have been entered onto the trial as a rifampicin sensitive subject on the rapid sputum based test result, who on receipt of the rifampicin resistance testing using an indirect susceptibility test in liquid culture, this shows a rifampicin resistant result.

- Subjects, who have been entered onto the trial as a fluoroquinolone sensitive subject on the rapid sputum based test result, who on receipt of the fluoroquinolone resistance testing using an indirect susceptibility test in liquid culture, this shows a fluoroquinolone resistant result.
- Lost to Follow-up.

In the case that a subject is withdrawn from the trial, and not Lost to Follow-up, subjects will be requested to attend the following trial visits:

- Early Withdrawal;
- Month 12 (if not already performed);
- Month 24;
- Additional visit, if required, for a ophthalmology examination (Table 12);
- Unscheduled Visits until a subject's primary outcome status has been defined (section 4.5.5).

The Month 12 and 24 visits will be to collect SAE information (including verification of survival) only and may be performed telephonically, at home or at the site.

If at any time the investigator is unsure whether or not to withdraw the subject, the investigator is to contact the sponsor medical monitor and discuss and agree on how the patient is to be handled.

For Lost to Follow up participants, a minimum of three contact attempts (telephonic/home visit) will be made. If these attempts are unsuccessful the subject will be considered lost to follow-up.

The Regulatory Authorities and Ethics Committees/Institutional Review Boards (EC/IRB) will be informed should the trial be terminated. All trial materials (except documentation that has to remain stored at the site) will be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

Early Withdrawal due to TB

Ultimately it is the investigator's decision whether a subject requires Early Withdrawal from the trial due to a concern that the subject has symptomatic worsening TB and/or bacteriological failure/relapse.

Early Withdrawal is usually not indicated for a single positive culture. Should a subject have a single positive culture result after being negative, the investigator is to evaluate whether the subject has signs and symptoms suggestive of active inadequately treated TB and whether it is in the subjects best interest that he/she be withdrawn. Prior to Early Withdrawal of a subject due to TB, the investigator must discuss the subject with the sponsor medical monitor, unless the investigator cannot contact the sponsor medical monitor and considers that Early withdrawal must occur immediately due to immediate safety concerns with respect to the subject.

If the investigator decides to withdraw a subject due to TB, additional sputum samples may need to be collected in order to ensure the subjects outcome status may be determined (section 4.5.5).

All Early Withdrawal subjects who are confirmed sputum positive (two sequential sputum positive cultures) and/or have symptomatic TB will require further TB treatment. These subjects will be referred to their applicable DS/MDR local community TB clinics for standard antituberculosis chemotherapy according to National TB Guidelines. The subjects will be provided with a referral letter to take with them to the TB Clinic. A follow-up call will be made by the trial site staff to the clinic to ensure the subject attended the clinic.

4.5.7.Stopping Rules

The trial or parts of the trial can be stopped or modified by the sponsor on the recommendation of the Data Safety and Monitoring Committee (DSMC) post their review of unblinded trial data which will occur at approximately six monthly intervals.

4.6. Subject Progress Definitions

All efforts should be made to contact subjects that do not attend scheduled trial visits. The investigator should attempt to follow up subjects that miss scheduled trial visits unless the subject has withdrawn consent.

If a subject fails to attend a scheduled trial visit, the site will attempt to contact the subject as soon as possible by phone (if applicable) and, if necessary, a home visit will be made, to encourage attendance at the earliest opportunity.

4.6.1. Enrolment

- **Screening Failure**

Subjects from whom informed consent is obtained and is documented in writing (that is, subject signs an informed consent form), but are not randomized.

- **Enrolled**

Subjects from whom informed consent is obtained and is documented in writing (that is, subject signs an informed consent form), and who are randomized (DS)/allocated (MDR) IMP.

4.6.2. Completed Trial

Enrolled subjects who complete Treatment and Follow-Up.

4.6.3. Withdrawn

- **During Treatment**

Enrolled subjects who withdraw/are withdrawn from the trial prior to completion of treatment visits.

- **During Follow-up**

Enrolled subjects who complete treatment, however withdraw/are withdrawn from the trial prior to completion of their follow-up visits.

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1. Trial Treatments

Subjects will receive oral, once-daily dosing. Table 13 details the five treatment arms and their applicable subject population.

Table 13: Treatment Groups

	Treatment Group	Subject Population
1.	Moxifloxacin 400 mg + PA-824 100 mg + pyrazinamide 1500 mg oral once daily for 17 weeks/4 months.	DS-TB
2.	Moxifloxacin 400 mg + PA-824 200 mg + pyrazinamide 1500 mg oral once daily for 17 weeks/4 months.	DS-TB
3.	Moxifloxacin 400 mg + PA-824 200 mg + pyrazinamide 1500 mg oral once daily for 26 weeks/6 months.	DS-TB

	Treatment Group	Subject Population
4.	Rifampicin 150 mg plus Isoniazid 75 mg plus Pyrazinamide 400 mg plus Ethambutol 275 mg combination tablets oral once daily for 8 weeks/2 months, followed by Rifampicin 150 mg plus Isoniazid 75 mg oral once daily for 18 weeks/4 months. The daily dose is per the subject's weight as follows: 30-39kg: 2 tablets; 40-54kg: 3 tablets; 55 – 70kg: 4 tablets; 71kg and over: 5 tablets.	DS-TB
5.	Moxifloxacin 400 mg + PA-824 200 mg + pyrazinamide 1500 mg oral once daily for 26weeks/6 months.	MDR-TB

All subjects in the HRZE/HR treatment arm will be given pyridoxine 10 mg daily as prophylaxis against peripheral neuropathy.

5.2. Method of Assigning Subjects to Treatment Groups

Eligible subjects who have given written, informed consent will be enrolled onto the trial during Days (Day -14(MDR)/-9(DS) to -1)(Screening) and will be identified by a trial generated subject identification code (subject number). Subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized (DS subjects) or assigned (MDR subjects) to a treatment number.

Central randomization will occur using an Interactive Voice and/or Web Response services (IVRS/IWRS) for subject enrolment and randomisation. As this is an open label trial there is no need for blinding or procedures to break the blind. The trial subjects, the site staff, sponsor and CROs will not be blinded to treatment assignment. However, it is planned that the applicable sponsor staff (such as medical monitors, trial statisticians (DSMC statisticians will be un-blinded), project managers, central radiologists, co-ordinating investigator), and bacteriology laboratory personnel will be blinded to treatment assignment, unless they need to know the treatment assignment in order to make decisions which effect the subjects safety or adverse event reporting requirements.

The IVRS/IWRS will utilize a dynamic randomization system using minimization with a random element.

Randomization/assignment may occur once all screening results are available and the investigator has determined that the subject is eligible for the trial. Once a subject is found to be eligible for the trial, the investigator will contact the IVRS/IWRS vendor and provide detail about the subject including their minimization factors. The randomization algorithm will allocate the subject to an intervention which will reduce the imbalance across the factors for those already randomized. It will include a random element to reduce the potentially deterministic nature of the method. The randomization algorithm including the random element will be validated prior to the first patient being enrolled into the trial. No fixed randomization list or pre-determined randomization schedule will be required to be generated.

Randomization/assignment may occur once all screening results are available and the investigator has determined that the subject is eligible for the trial.

5.3. IMP Administration

IMP will be taken once a day, as follows:

- For the MPaZ treatment arms, IMP will be taken with a full glass of water.
- For the HRZE/HR treatment arm, IMP will be taken with a full glass of water at least 1 hour before or 2 hours after a meal.

5.4. Subject Compliance

Sites will be responsible for ensuring subject IMP compliance. Compliance to treatment will be recorded in the subject's eCRF and in the source documents. IMP administration will be supervised per local site practice to assure compliance to regimen.

The importance of adherence to the treatment schedule will be reinforced at each visit. Non-adherence should prompt the investigator to identify and address the cause(s) (e.g. side effects) of the non-adherence and contact the sponsor medical monitor. Subjects missing:

- ≤ 7 consecutive doses of IMP doses: restart IMP, no extension of IMP required.
- 7 to ≤ 21 consecutive doses of IMP: restart IMP, extend the IMP treatment by the number of consecutive doses missed.
- > 21 consecutive doses of IMP, discontinue IMP and withdraw subject from the trial.

Any subject for whom the trial medication is discontinued (including for non-adherence) will be discussed with the sponsor medical monitor and, if applicable, the subject will be restarted on trial medication as soon as possible.

5.5. Blinding and Procedures for Breaking the Blind

As this is an open label trial there is no need for blinding or procedures to break the blind. The trial subjects, the site staff, sponsor and CROs will not be blinded to treatment assignment. However, it is planned that the applicable sponsor staff (such as medical monitors, trial statisticians (DSMC statisticians will be un-blinded), project managers, central radiologists, co-ordinating investigator), and bacteriology laboratory personnel will be blinded to treatment assignment, unless they need to know the treatment assignment in order to make decisions which effect the subjects safety or adverse event reporting requirements.

5.6. IMP Packaging and Labelling

The complete formulations and description of the IMP are found in the applicable Investigator Brochures [7] and Package Inserts [11, 12, 22, 23].

5.6.1. Packaging

Subjects will receive the following IMP, depending onto which group they are randomized/assigned (Table 14).

Table 14: Investigational Medicinal Product Details

Subject Population	Treatment Group	Product Details
DS-TB	Moxifloxacin plus PA-824 plus pyrazinamide (17 weeks/4 months).	Days 1-119: 1 moxifloxacin 400 mg + 1 PA-824 100 mg tablet + 3 pyrazinamide 500 mg tablets once daily.
DS-TB	Moxifloxacin plus PA-824 plus pyrazinamide (17 weeks/4 months).	Days 1-119: 1 moxifloxacin 400 mg + 1 PA-824 200 mg tablet + 3 pyrazinamide 500 mg tablets once daily.
DS-TB	Moxifloxacin plus PA-824 plus pyrazinamide (26 weeks/6 months).	Days 1-182: 1 moxifloxacin 400 mg + 1 PA-824 200 mg tablet + 3 pyrazinamide 500 mg tablets once daily.

Subject Population	Treatment Group	Product Details
DS-TB	HRZE (8 weeks/2 months) followed by HR (18 weeks/4 months).	Days 1-56: Rifampicin 150 mg plus Isoniazid 75 mg plus Pyrazinamide 400 mg plus Ethambutol 275 mg combination tablets oral once daily Days 57-182: Rifampicin 150 mg plus Isoniazid 75 mg oral once daily. The daily dose is per the subject's weight as follows: 30-39kg: 2 tablets; 40-54kg: 3 tablets; 55 – 70kg: 4 tablets; 71kg and over: 5 tablets
MDR-TB	Moxifloxacin plus PA-824 plus pyrazinamide (26 weeks/6 months).	Days 1-154: 1 moxifloxacin 400 mg + 1 PA-824 200 mg tablet + 3 pyrazinamide 500 mg tablets once daily

5.6.2.Labelling

The IMP Arms will be packaged in individual treatment packs. The outer packaging of each treatment pack will be labelled with, at a minimum, the following information:

- Name of Sponsor and Address;
- Trial number;
- Name of medication;
- Dosage, quantity and method of administration;
- Reference/Lot Number;
- Treatment Number;
- Directions for use;
- The statement "For Clinical Trial Use Only";
- Space for completion of Name of Investigator and Site Number;
- Storage conditions;
- Period of Use;
- The statement "Keep out of reach of children";
- Expiry Date.

The inner packaging of each treatment pack will be labelled with, at a minimum, the following information:

- Name of Sponsor and Address;
- Trial number;
- Name of medication;
- Dosage, quantity and method of administration;
- Reference Number;
- Treatment Number;
- Directions for use;
- The statement "For Clinical Trial Use Only".

5.7. Storage

All trial medication will be kept securely stored by the site pharmacist/delegated dispenser in a secured area with limited access to designated site personnel only.

MPaZ treatment arms IMP will be stored in the supplied containers, protected from moisture, between 15 to 30 degrees Celsius.

HRZE/HR treatment arm IMP will be stored at <25 degrees Celsius, per the manufacturers Package Insert, in the tightly closed container that is supplied in, protected from light.

5.8. Dispensing and Accountability

The site pharmacist/delegated dispenser will be responsible for dispensing the IMP. Accurate accountability records will be kept by the site to assure that the IMP will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol i.e. delivery to site, inventory at site, use by subject, destruction etc. The investigator/designee will immediately inform the sponsor of any quality issues arising with respect to the IMP. The sponsor will take whatever action is required should such a situation arise.

The investigator undertakes to use the IMP only as indicated in this protocol.

5.9. Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used IMPs must be returned to sponsor (or designated contractor).

6. TRIAL VARIABLES AND PROCEDURES

Semen sub-trial test parameters will be described in the separate semen sub-trial protocol.

6.1. Demographic and Background Variables and Procedures

The following demographic and background variables will be collected at the time points described in the trial flow chart:

- Visit Dates.
- Subject Disposition.
- Written Informed Consent (including HIV consent).
- Demography: Date of birth, race, and gender.
- Clinically significant medical, treatment and smoking history.
- Inclusion and exclusion criteria.
- Two Screening Spot Sputum: (at the research site under the coaching and observation of the trial staff)
  The Mycobacteriology sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed on one of these samples. The second sample is collected as a back-up sample to the first sample in case it is not possible to obtain a result/s on the first sample:
  - Direct microscopy for acid-fast bacilli;
  - Rapid test for fluoroquinolones and rifampicin resistance;
  - Extracted bacterial DNA molecular test for pyrazinamide resistance.
- Serology: HIV status and CD4 count.
  - HIV and CD4 count: Approval for this to be performed will be obtained from subjects in the written informed consent process. If an HIV test [ELISA and/or Western Blot and/or Electro-Chemiluminescence], was performed within 1 month prior to screening, it should not be repeated as long as documentation can be provided. Prior to HIV testing and on receipt of the results, subjects will be counseled on HIV by trained counselors. HIV counselling should be clearly documented in the

subject's medical records/source. Subjects have the right to decline to know or receive their HIV test results. This decision should be clearly documented in the subject's medical records/source. CD4 count to be performed on HIV-positive subjects only.

- Karnofsky Score (Appendix 2).
- Serum pregnancy test (women of child-bearing potential only, whether they are sexually active or not).
- Chest X-ray. A chest x-ray picture will be obtained from the clinic appointed radiology department. The investigator is responsible for its review and analysis for subject inclusion and randomisation stratification. Images will also be collected and read centrally. This will be described in a separate document, the Radiology Manual.
- IMP Randomization/Assignment.
- IMP Compliance.

6.2. Efficacy Variables and Procedures

The following efficacy variables will be collected at the time points described in the trial flow chart.

- Screening Spot Sputum x 2 (at the research site under the coaching and observation of the trial staff) and Sputum Sample collection x 2 (one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff).
  The Mycobacteriology sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
  - Culture result (MGIT);
  - TTP in liquid medium (MGIT);

  Using these observed variables the following derived variables will be assessed for evaluation of the efficacy endpoints:
  - Bacteriologic failure/relapse;
  - The rate of change in log time of sputum culture positivity (TTP) over time in liquid medium;
  - Time to Sputum Culture Conversion;
  - Number of subjects with Sputum Culture Conversion.

  Every effort is to be made to collect sputum samples. However, in general, the inability to produce sputum is treated as being equivalent to having a negative culture (favourable) result. A subject who never achieves culture negative status due to inability to produce sputum, after TB confirmation via culture has been confirmed on the applicable baseline sample, but has completed 12/24 months follow-up and is without clinical or biological evidence of relapse, will be considered to have a favorable outcome.

- TB Symptoms Profile
  The TB Symptoms Profile (Appendix 7) variables will be collected at the time points described in the trial flow chart. It will record subjects' ratings of the severity of common TB symptoms.
- Patient Reported Health Status Variables and Procedures.
  The Patient Reported Health Status variables will be collected at the time points described in the trial flow chart. Patient Reported Health Status will be collected using the EQ-5D-5L Health Questionnaire (Appendix 8). This descriptive system consists of five health-related quality of life dimensions, each of which will be recorded using five levels of severity.
  Methodology: The Patient Reported Health Status methodology and requirements will be described in a separate document/guideline which will be provided prior to the trial start.

6.3. Safety and Tolerability Variables and Procedures

The following procedures and testing will be performed at the time points described in the trial flow chart:

- Safety Laboratory Test Parameters:
  - Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count.
  - Clinical Chemistry: Albumin, urea, creatinine, direct, indirect and total bilirubin, uric acid, total protein, ALP, AST, ALT, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), phosphate, sodium, potassium, calcium (corrected for albumin), chloride, random/fasting glucose, bicarbonate/CO_2. Creatinine Clearance to be calculated at screening using Cockcroft-Gault Formula (Appendix 5).
    Note: It is preferable for a fasting glucose to be obtained at screening. However if the subject arrives at the screening visit not in a fasting condition, a random glucose may be done. If the resulting glucose is significantly elevated (>11.1 mmol/L) the following procedures must be followed during screening:
    - The investigator is to question the subject about possible clinical symptoms and look for possible clinical signs of diabetes.
    - The urinalysis glucose results are also to be taken into consideration.

    If based on these results, it is the opinion of the investigator that the subject may have a significant endocrine abnormality the subject should not be enrolled (screening failure).
  - Serum Endocrinology (Males subjects only): testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and Inhibin B.
  - Urinalysis; pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes. Microscopy may be completed to follow up abnormal urinalysis results at the discretion of the investigator.

  Sample Collection Methodology: The sample collection methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided to the site prior to trial start.
- Vital signs:
  - Systolic and diastolic blood pressure (mmHg) to be measured supine (after 5 minutes of rest) using an appropriately sized cuff, and using the same type of sphygmomanometer, if possible by the same observer, at each relevant visit.
  - Heart rate (bpm).
  - Axillary body temperature (°C).
- Physical Examination:
  - Height is measured at screening only.
  - Full (complete) and Limited (pulmonary, cardiovascular and abdominal) examinations will be performed and any clinically significant findings will be recorded.
  - Weight (kg) (in light clothing and with no shoes).
  - Using the observed variables weight and height, calculated body mass index (BMI) will be derived.
- 12-lead ECG:
  - Investigator Assessment: Normal, Abnormal.
  - Central Cardiologist Assessment: Heart rate, PR interval, RR interval, QT, corrected QT Interval (QTc) (QTcB and QTcF), QRS.

  Methodology:
  - Timing and registration technique for ECGs will be standardized for all subjects and will be described in a separate document which will be provided prior to the trial start;
  - Subjects should be lying down (recumbent) 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 single.

For each subject, the ECGs should, to every extent possible, be collected at approximately the same time of day and in the same fed/fast state (e.g. 4 hours after lunch).

- Ophthalmological Examination:
  - Ophthalmology History.
  - Visual Acuity Test – corrected. Near and Distance Vision.
  - AREDS2 opacity typing and grading.

  Methodology: The Ophthalmology methodology and requirements will be described in a separate document, the Ophthalmology Guideline, which will be provided prior to the trial start.
- Concomitant medications.
- Adverse Events.

6.4. PK Variables and Procedures

The following pharmacokinetics variables will be collected at the time points described in the trial flow chart:

- Plasma Concentrations of M, Pa and Z.

Methodology: The PK Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start.
No PK variables will be collected or derived on the HRZE/HR treatment arm.

6.5. Mycobacterial Characterization:

The following Mycobacterial Characterization variables will be collected:

Performed:

- Day 1 (baseline) sputum sample (or screening or out to Week 4 if the baseline is contaminated or negative);
- Positive Cultures at or after Week 17 (4 month treatment arms)/Week 26 (6 month treatment arms).

The *MTB* isolates will be processed for:

- Speciation of the infecting organisms by molecular or antigen based test to confirm MTB;
- MIC against moxifloxacin and PA-824;
- Drug Susceptibility Testing for rifampicin, isoniazid, ethambutol, moxifloxacin, and pyrazinamide using an indirect susceptibility test in liquid culture;
- Extraction of organismal (*MTB*) DNA for molecular strain typing.

All Day 1 (baseline) *MTB* isolates and isolates from positive cultures to be stored at the local microbiology laboratory. The extracted *MTB* DNA and isolates will be stored for potential further work to validate new assay tools for a maximum of 5 years after trial closure. The Mycobacteriology sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start.

7. ADVERSE EVENTS

The investigators are responsible for eliciting adverse events by observing the subject and recording all adverse events observed by him/her or reported by the subject during the trial.

7.1. Definitions

7.1.1.Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

7.1.2.Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death;
- is life threatening (any event in which the subject 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;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event.

Note:

Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. A "suspected transmission of infectious agent by a medicinal product" is also considered a serious adverse event under the SAE criterion "Other medically important condition".

7.1.3.Unlisted (Unexpected) Adverse Event

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

7.1.4.Life threatening

Any event in which the subject 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.

7.1.5.Associated with the Use of the Drug

An adverse event is considered associated with the use of the drug (Adverse Drug Reaction) if the attribution is possible, probable or very likely.

7.1.6.Attribution/Causality

See Table 15 for the definitions for rating attribution/causality.

Table 15: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An adverse event, which is not related to the use of the drug.
Doubtful	An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Relatedness Rating	Definition
Possible	An adverse event, which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.
Probable	An adverse event, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by dechallenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Very Likely	An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

7.1.7.Severity

Severity rating is to be made per the DMID Adult Toxicity Table (Appendix 4). For abnormalities **NOT found** in the Toxicity Tables the scale described in Table 16 is to be used to estimate grade of severity:

Table 16: Adverse Event Severity Ratings

Severity Rating	Definition
Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible.
Potentially Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care probable.

7.1.8.Other AE Definitions

The following definitions will be used for Adverse Event Reporting:

Action Taken with IMP

- IMP unchanged
- IMP interrupted
- IMP stopped
- Not applicable (Follow-up period)

Other Action Taken

- None
- Medication given
- Hospitalisation or prolongation of hospitalisation
- Therapeutic or diagnostic procedure

Outcome

- Resolved
- Improved
- Unchanged
- Worse
- Fatal
- Unknown

Occurrence

- Once
- Intermittent
- Continuous

7.2. Reporting

7.2.1.Adverse Event (AE)

Adverse events will be collected by the investigator from the time a subject signs the Informed Consent Form through to their Month 24 follow-up visit. The exception to this is Early Withdrawal subjects who will only have SAEs collected from their time of Early Withdrawal to their Month 24 follow-up visit.

Any AE (serious or non-serious) observed by the investigator or reported by the subject will be recorded on the Adverse Event Case Report Form. The investigator will review each AE and assess its relationship to drug treatment based on all available information at the time of the completion of the case report form. The following information will be recorded for each Adverse Event reported (definitions section 7.1):

- Diagnosis of the AE, if possible. In the case where an overall diagnosis cannot be made, each specific sign and/or symptom will be recorded as individual AEs;
- Date of onset;
- Stop Date (duration) if applicable;
- Severity;
- Action Taken with IMP;
- Other Action Taken;
- Outcome;
- Relationship to IMP;
- Occurrence;
- Seriousness.

7.2.2.Serious Adverse Event (SAE)

Any AE that occurs which is serious must be reported by the investigator to the trial monitor and copied to the sponsor Medical Monitor within 24 hours of the site first being aware of the SAE, whether or not the serious event is deemed associated with the use of the drug.

In addition, the investigator will provide a detailed, signed, written, and complete SAE report form that addresses the investigator's estimates of the attribution/causality of the AE to the trial drug and the seriousness of the AE in question to the trial monitor and sponsor medical monitor within 24 hours of becoming aware of the SAE.

The trial monitor will confirm receipt of the SAE Form with the investigator and review the initial information on the SAE for diagnosis, consistency and completeness of data.

For submission of updated or additional information on a previously reported SAE, the investigator will provide the trial monitor and sponsor medical monitor with a newly completed Serious Adverse Event Form, designated as a follow-up report. This will be submitted to the trial monitor and sponsor medical monitor within 24 hours of the investigator receiving the information.

The trial monitor will query for additional information from the investigator, if necessary, to complete the profile of the SAE reported.

The sponsor/investigator/designee will inform Regulatory Authorities and/or IEC/IRB of all SAEs in accordance with local requirements and ICH guidelines for GCP.

The sponsor/designee will forward Safety Notification letters to the investigator for submission to the IEC/IRB.

7.2.3.Follow up of Adverse Events

All AEs 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.

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. However, this will have to be agreed upon with the TB Alliance.

7.2.4.Post-Trial Adverse Events

Any new SAEs reported by the subject to the investigator that occur after the last scheduled contact, and are determined by the investigator to be possible, probable or very likely related to the use of the IMP, will be reported to the sponsor, IEC/IRB and regulatory authorities on an expedited basis as required in accordance with local requirements and ICH guidelines for GCP.

7.2.5.Clinical Laboratory Adverse Events

Changes in the results of the Clinical Laboratory assessment results which the investigator feels are clinically significant will be reported as adverse events. It is the investigators' responsibility to review the results of all laboratory tests as they become available. This review must be documented by the investigators' dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain and document if this is a clinically significant change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is determined by the investigator to be a clinically significant change from baseline for that subject, it is considered to be an adverse event.

7.2.6. Disease under Study

Symptoms of the disease under study (Tuberculosis) experienced by the subject while on the trial will be assessed by the investigator. If the symptom has:

- worsened while the subject is in the trial; and
- the investigator assesses it as clinically significant;

it will be recorded as an adverse event.

If there is:

- no change; and
- the investigator assesses the symptom as due to the subject's TB; and
- not clinically significant;

it will not be recorded as an AE and this will be noted in the subject's source documentation.

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

7.2.7. Overdose

Overdose of IMP experienced by the subject while on the trial, will be assessed by the investigator to determine whether the overdose led to an Adverse Event, including if the taking of the suspect medicine led to suicidal intention and subsequent overdose of the suspect medicine, or other medication. In this case it will be recorded as an adverse event. If it does not lead to an Adverse Event it will not be recorded as an AE and this will be noted in the subject's source documentation.

7.2.8. Drug Interaction

If the investigator becomes aware that the subject has experienced a drug interaction which has resulted in an adverse event, it will be recorded as an adverse event.

7.2.9. Pregnancy

The investigator will immediately notify the sponsor of any pregnancy that is discovered during IMP administration or which started 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 the sponsor follow-up information regarding the outcome of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for 6 months.

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) for the following time-periods:

- During IMP administration or which started during IMP administration;
- During the Follow-up Period .

If pregnancy is suspected while the subject is receiving IMP, the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner and the subject withdrawn from the trial. Protocol-required procedures for trial discontinuation and follow-up will be performed unless contraindicated by the pregnancy.

Should the female partner of a male subject become pregnant during the trial or in the 12 weeks after the completion of IMP and the investigator becomes aware that this situation has occurred, consent will be requested from the female partner for collection of information on her pregnancy history and for information on the current pregnancy and birth.

Pregnancy reporting will **follow the same time lines and reporting structures as for a SAE** (see above). SAE reporting will also occur if the pregnancy outcome is a congenital anomaly. This will follow the reporting procedures described above for SAE reporting plus an additional clinical report compiled by the applicable company.

7.3. Monitoring and Safety for Specific Toxicities

AEs still on-going at the end of treatment 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. The exception to this is all grade 3 and grade 4 laboratory abnormalities and laboratory abnormalities resulting in an increase of 2 grades from baseline will be followed until return to baseline or within one grade from baseline (Appendix 4).

Note: For grade 3 or 4 laboratory toxicities, subjects should have a confirmatory measurement within 48 hours where possible. This management scheme is for confirmed lab abnormalities and not for isolated events.

Monitoring for specific toxicities are based upon target organs defined in preclinical toxicity trials (see Investigator's Brochures and Package Inserts [7, 11, 12, 22, 23].

Note: If a subject misses more than 21 consecutive doses of IMP, IMP is to be discontinued and the subject withdrawn from the trial (section 0).

7.3.1. Hepatic Toxicity

Management of hepatic toxicity is described in Appendix 9.

7.3.2. Cardiac Rhythm Disturbances

Subjects with a:

- Grade 1 (asymptomatic) or Grade 2 (asymptomatic, transient rhythm abnormality not requiring any treatment) cardiac rhythm disturbances:

  Subjects may continue IMP and should be carefully evaluated and followed closely.

- Grade 3 (recurrent, persistent, symptomatic arrhythmia requiring treatment) or Grade 4 (unstable dysrhythmia requiring treatment) cardiac rhythm disturbances:

  IMP should be withheld and the sponsor medical monitor should be contacted to consider whether the subject should permanently discontinue IMP and be withdrawn from the trial.

- If on centralized ECG reading and interpretation a subject has:
  - QTcF ≥ 500 msec, or
  - they develop a new left bundle branch block (LBBB) or Mobitz type 2 or complete heart block;

  the ECG should be repeated and confirmed by the centralized cardiology reading and interpretation. If these findings are confirmed, IMP should be withheld and the sponsor medical monitor should be contacted, to discuss and agree on how the patient is to be handled.

7.3.3. Gastrointestinal Disturbances

Subjects with Grade 4 elevation of gastrointestinal parameters will not be withdrawn from the trial, however should be monitored closely.

7.3.4.Other toxicities

Refer to Appendix 4.

- **Grade 1 or 2**

Subjects who develop grade 1 or 2 AE or laboratory toxicity may continue intake of IMP.

- **Grade 3 or 4**

Subjects who develop grade 3 or 4 AE or laboratory toxicity will be carefully evaluated by the investigator. Subjects may continue intake of IMP or be withdrawn from the trial if, in the opinion of the investigator, the AE or laboratory toxicity poses a significant risk for the subject in case of continued participation in the trial. Subjects should be followed as appropriate until resolution of the AE or toxicity.

7.4. Safety Monitoring by the Data Safety Monitoring Committee

A DSMC will be appointed for the trial. The primary responsibility of the DSMC will be to act in an advisory capacity to the sponsor to safeguard the interests of trial subjects by monitoring subject safety, assess subject risk versus benefit, assess data quality and general evaluation of the trial progress. It's 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 the sponsor and the trial team. It will comprise at least 3 voting members. The DSMC may have an organisational meeting prior to commencement of the trial. The DSMC will meet approximately every six months and at least annually when it will review unblinded data during a closed session. The sponsor or the DSMC may convene ad hoc meetings if safety concerns arise during the trial. After its assessment, the DSMC will recommend to the sponsor continuation, modification or termination of the clinical trial.

8. STATISTICAL ANALYSIS

A general description of the statistical methods planned to be used to analyze efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP) which will be written and signed off prior to the First Patient In.

8.1. Method of Randomization

DS-TB subjects will be randomised to one of the four regimens in a 1:1:1:1 ratio, using IVRS/IWRS which will utilize a dynamic randomization system using minimization with a random element. The system will be controlled through an authorised user name and password. Before treatment allocation, the patient's eligibility will be confirmed, and the minimisation factors entered into the database.

8.2. Primary outcome measures and analysis populations

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT) and will evaluate the hypothesis that in the subjects with DS-TB in any arm of the experimental MPaZ treatment regimens the incidence of bacteriologic failure or relapse or clinical failure when the last enrolled subject has completed 12 months from the start of therapy, is non-inferior to the proportion observed in patients who are treated with the standard HRZE/HR regimen. Note the primary analysis will be restricted to those who are not isoniazid mono-resistant at baseline.

Both a Modified Intent to Treat (MITT) and a Per Protocol (PP) analysis will be conducted. The proposed primary outcome status is described in section 8.5.1. Details of subjects excluded from the MITT and PP analysis will be described in detail in the SAP.

Every effort will be made to obtain cultures for primary endpoint assessment, including bringing the patient back for a repeat visit if necessary. In the rare event that this will not be possible, and clinical information is also

missing at the final scheduled visit, these patients in general will be considered unassessable. If the reason for the missing sample was an inability to produce sputum, this will generally be considered a favourable outcome. Further details will be provided in the SAP.

The safety and tolerability analysis will include all subjects who were randomized to and received at least one dose of the IMP.

Full details of all analysis populations, including All Randomised and All Randomised Excluding Late Screening Failures, and sensitivity analyses for different ways of handling the unassessable data will be described in the SAP.

8.3. Sample Size

The following assumptions have been made in calculating the numbers of subjects needed for the primary endpoint analysis.

- The unfavorable rate in the control regimen will be 16%, consistent with the control arm unfavourable rate in a recent Phase 3 TB trial.
- An unassessable rate of 15%, consistent with the overall unassessable rate in a recent Phase 3 TB trial.
- An additional 8% excluded for isoniazid mono-resistance, consistent with the overall percentage observed in a recent Phase 3 TB trial.
- An acceptable non-inferiority margin (delta) is 12% (section 8.5);
- The power to demonstrate non-inferiority is 90% and the significance is 2.5% (1-sided).

Under these assumptions we would require 255 subjects for each treatment arm, giving a total sample size of 1,020 DS-TB subjects. Although these are considered to be reasonable assumptions based on recent data, in order to allow for the possibility of higher unfavorable and/or unassessable rates, or somewhat greater than 8% of subjects with INH mono-resistance, 300 DS-TB subjects will be recruited to each randomized arm giving a total of 1,200 subjects with DS-TB. Note that the primary analysis of the DS-TB subjects will exclude the subjects with isoniazid mono-resistance. There is no formal statistical analysis planned for the MDR-TB group. The plan is to enroll up to or equal to 300 MDR-TB subjects.

8.4. Interim Analyses

No formal interim analyses are planned. Primary analysis will be performed on the 12 month data (after the start of therapy when the last enrolled subject has completed 12 months from the start of therapy).

There will be either two/three/four database locks, data analyses and trial reports generated for this trial, depending on the MDR-TB recruitment rate:

1. When all DS-TB subject have completed 12 months follow-up from start of therapy. This will be used for submission for Market Authorization Approval.
2. When all DS-TB subjects have completed 24 months follow-up from start of therapy.
3. When MDR-TB recruitment is closed and subjects have completed 12 and/or 24 month follow up from start of therapy.

8.5. Primary Endpoint Analysis

The primary efficacy endpoint is the incidence of bacteriologic failure or relapse or clinical failure at 12 months from the start of therapy.

The primary efficacy analysis in the DS-TB treatment groups will include three comparisons, a non-inferiority comparison of each of the 3 experimental MPaZ treatment arm with the standard HRZE/HE treatment arm. Non-inferiority will be assessed using the upper bound of the one-sided 97.5% confidence interval for the difference between the proportion of subjects who are classified as having an unfavourable status on the intervention less the control regimen. If the upper bound of the one-sided 97.5% confidence limit for this

difference in proportions is less than 12% (the margin of inferiority) the intervention will be considered to be non-inferior to control arm of the comparison.

The first hypothesis to be tested will be the 6 month experimental regimen against the standard regimen. The second hypothesis to be tested will be the PA-824 200mg 4 month experimental regimen against the standard regimen. The third hypothesis to be tested will be the PA-824 100mg 4 month experimental regimen against the standard regimen. To preserve the type I error rate, the second hypothesis will only be tested if non-inferiority is demonstrated with the 6 month experimental regimen. Similary the third hypothesis will only be tested if non-inferiority of the PA-824 200mg 4 month regimen has been demonstrated. This hierarchical testing strategy means no adjustments are required for multiple comparisons.

Note, the primary analysis will be restricted to those who are not isoniazid mono-resistant at baseline, but will include those who are rifampicin mono-resistant.

8.5.1. Classification of primary status

The primary analysis will be conducted using culture results from liquid culture (MGIT) media.

Subjects will be classified as having a favorable, unfavorable or unassessable outcome status which will be defined in detail in the SAP. In general, subjects achieving and maintaining culture negative status without any additional treatment will be considered favorable; subjects who fail on treatment or relapse in follow-up will be considered unfavorable and subjects who are not assessable (and who have not already been declared as unfavorable) will be considered unassessable and excluded from the analysis.

8.5.2. Secondary Endpoint Analyses

8.5.2.1. Efficacy Analysis

The secondary efficacy endpoints and analyses are as follows are:

- Incidence of bacteriologic failure or relapse or clinical failure at 24 months from the start of therapy as a confirmatory analysis.
- The rate of change in time of sputum culture positivity (TTP) over time in liquid culture (MGIT) in sputum represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time to be explored as a potential biomarker of definitive outcome.
- Time to sputum culture conversion to negative status in liquid culture (MGIT) through the treatment period to be explored as a potential biomarker of definitive outcome.
- Proportion of subjects with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 8, 12 and 17 weeks to be explored as a potential biomarker of definitive outcome.
- Proportion of subjects experiencing a change from baseline in TB symptoms.
- Change from baseline in Patient Reported Health Status will be analysed and presented.

The effect of baseline covariates will be explored, including but not limited to the presence or absence of cavities on Chest X-ray from a central reading, the presence or absence of HIV infection, and site or geographic region.

Exploratory analyses will include a separate analysis of the isoniazid and rifampicin mono-resistant patients.

The details of these analyses will be described in the SAP which will be written and signed off prior to First Patient In.

8.5.3.Safety and Tolerability Analysis

The following will be analyzed and presented:

- Adverse Events
  - All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by Preferred Term within each MedDRA System Organ Class (SOC).
  - The incidence of the following events will be summarized by treatment group for further medical analysis:
    - Incidence of Treatment-emergent adverse events (TEAEs);
    - Incidence of TEAEs by Severity;
    - Incidence of Drug-Related TEAEs;
    - Incidence of Serious TEAEs;
    - Incidence of TEAEs Leading to Early Withdrawal;
    - Incidence of TEAEs leading to Death.
- Clinical Safety Laboratory Measurements
  Quantitative and qualitative measurements, including observed and change from baseline, will be presented.
- Cardiovascular Safety (Appendix 10).
  - ECGs will be centrally read.
  - Quantitative and qualitative measurement of ECG results (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval), including observed and change from baseline, will be presented.
  - QT intervals will be adjusted using Fridericia's correction and Bazett'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 group and time of collection. For IMP containing treatment arms, the potential correlations between the plasma concentration of IMP and the change from baseline of QT interval corrected by Fridericia's method (QTcF) and change from baseline of QT interval corrected by Bazett's method (QTcB) with respect to time for the different treatment groups will be explored. These will be presented as descriptive analyses, and no inferential tests will be carried out.
    - Post-baseline QT/QTc intervals will be classified into the following categories:
      - QT/QTc < 450 msec
      - 450 msec $\leq$ QT/QTc < 480 msec
      - 480 msec $\leq$ QT/QTc < 500 msec
      - QT/QTc $\geq$ 500 msec
    - QTc changes from baseline will be classified into the following categories:
      - increase < 30 msec,
      - $\geq$ 30 msec and < 60 msec, and
      - increase $\geq$ 60 msec.

    Frequency counts will be used to summarize the number of subjects at each time point according to the above categories.
  - ECG results will be classified as normal or abnormal (investigator assessment) and summarized using frequency counts by dose group and time of collection.
- Ophthalmology: Descriptive statistics will be presented for ophthalmology slit lamp examination data (AREDS2 lens opacity classification and grading) and listed by patient. Categorical data for lens opacity will be summarized in a frequency table for the left and right eye, respectively.
- Changes in male reproductive hormones will be presented.

- Semen sub-trial analyses will be described in the separate semen sub-trial protocol.
- Other safety variables: Physical Examination, Vital signs (Appendix 10), Concomitant medication. Descriptive summary statistics will be presented.

8.5.4.Pharmacokinetics (PK)

Plasma concentrations from sparse sampling will be used to build a population PK model to evaluate the effects of baseline subject covariates on trial drug pharmacokinetics and associated bacteriological endpoints. PK samples from the Phase 2 trials with more frequent PK sampling will be used along with the PK samples in this trial to build the model.

No PK analyses will be performed on the HRZE/HR treatment arm.

8.5.5.Pharmacokinetics-Pharmacodynamics (PK-PD)

Population PK models will be developed using the pre-dose (trough) plasma concentrations of each drug in the combination drug regimen. These population PK models will be used to explore trends in the safety and efficacy data from the trial, and will be presented in a separate report to the Clinical Trial Report for this trial.

No PK-PD analyses will be performed on the HRZE/HR treatment arm.

8.5.6.Mycobacterial Characterization:

Descriptive summary statistics of the mycobacterial characteristics of the subjects' *MTB* strains assessed will be presented.

9. RECORDS MANAGEMENT

9.1. Data Collection

All CRF/eCRF pages will be completed for each subject who receives any amount of IMP. For screening failure subjects a screening failure CRF will be completed. For subjects who are prematurely withdrawn, the visits up to withdrawal plus the withdrawal and follow-up visits need to be completed.

9.2. Source Documents

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, electronic data, screening logs, and recorded data from automated instruments.

All source documents pertaining to this trial will be maintained by the investigators. The investigator has to permit trial-related monitoring, audits, Independent Ethics Committee/Institutional Review Board (IEC/IRB) review and regulatory inspections providing authorized persons direct access to source documents.

9.3. File Management at the Trial Centre

It is the responsibility of the investigators to ensure that the trial center files are maintained in accordance with International Good Clinical Practice Guidelines and the ethical principles that have their origin in the Declaration of Helsinki.

9.4. Records Retention at the Trial Centre

The investigator is obliged to retain records and data from the trial for safety reasons and for audit and inspection subsequent to trial completion. The essential documents should be retained for not less than 5 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 5 years have elapsed since the formal discontinuation of clinical development of the IMP.

The sponsor will make financial provisions for the investigator to deposit the documents at an external site for safekeeping for as long as required by regulations and the sponsor.

10. QUALITY CONTROL AND ASSURANCE

10.1. Site Procedures

The investigator undertakes to perform the clinical trial in accordance with this protocol, International GCP, and the ethical principles that have their origin in the Declaration of Helsinki and applicable regulatory requirements.

The investigator undertakes to complete the CRFs according to the sponsor's requirements, in a timely, accurate and legible manner. CRF entries will be verifiable to source documentation other than the CRF, as described in the applicable trial instructions.

Site Standard Operating Procedures will be adhered to for all clinical and bioanalytical activities relevant to the quality of the trial. Subject compliance will be monitored throughout the trial.

The investigator will sign and date any analysis results (e.g. laboratory, ECG, etc.) to verify that the results have been reviewed.

The investigator may appoint other sub-investigators to assist with the trial. However the investigator maintains responsibility for the trial and will supervise the sub-investigators. Written IEC/IRB approval will be obtained prior to involvement in the trial.

The investigator will ensure that all site personnel are adequately trained in GCP, the protocol, IB and all trial procedures and requirements.

10.2. Monitoring

The investigator is responsible for the validity of all data collected at the clinical site and must accept the various monitoring procedures employed by the sponsor. The purpose of monitoring is to verify that the rights and well-being of human subjects are protected; that trial data are accurate, complete and verifiable with source data; and that the trial is conducted in compliance with the protocol, International GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

Monitors assigned by the sponsor will conduct regular site visits for the purpose of monitoring various aspects of the trial. Visits will take place usually within a predetermined interval, but this may vary during the course of the trial. The investigator and site staff will allow the trial monitor and authorized representatives of the sponsor to (1) inspect all CRFs, written informed consent documents and corresponding source documents (e.g. original medical records), subject records and laboratory raw data, and (2) access clinical supplies, dispensing and storage areas. The investigator and site staff should also (1) agree to assist with monitoring activities if requested and (2) provide adequate time and space for monitoring visits.

The monitor will query any missing, confusing, spurious, or otherwise ambiguous data with the investigator. All queries should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor's signature and investigator or designee's confirmation signature.

10.3. Auditing

For the purpose of compliance with International GCP and regulatory agency guidelines, it may be necessary for sponsor-authorized Quality Assurance personnel and/or authorized personnel from an external regulatory agency to conduct an audit or inspection of the investigational site. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy and consistency, and to assure that trials are in accordance with the guidelines. Having the highest quality data from trials is an essential aspect of drug development.

The investigator and site staff will be given sufficient notice to prepare for such visits, which will usually last between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all trial-related supplies; and source documents against the CRFs to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred.

In the event of the site being notified of a Regulatory Inspection, the sponsor will help with preparation. It is essential that the sponsor be notified of the inspection as soon as possible.

11. ETHICS AND REGULATORY

11.1. Basic Principles

This research will be carried out in accordance with International GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

11.2. Independent Ethics Committee/Institutional Review Board (IEC/IRB) Review

The Investigator's/institution's written application to the IRB/IEC will include the approved protocol, written informed consent, any written information to be provided to the subject or any modification thereof, plus any other study related documents required for review. The protocol and all the required study related documents will be reviewed by the sites' respective IEC/IRB. The study will not start at a site until the IEC/IRB has approved all the relevant documents. As part of the Investigator's/institution's written application to the IRB/IEC, the Investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure or Package Insert. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC. During the trial the Investigator/institution should provide to the IRB/IEC all documents subject to review.

The IEC/IRB shall be constituted and shall operate in accordance with International GCP and the ethical principles that have their origin in the Declaration of Helsinki . The Investigator will maintain an accurate and complete record of all submissions made to the IRB/IEC. The records should be filed in the Investigator's Study File, and copies will be sent to the Sponsor.

11.3. Regulatory Authorities

The Regulatory Authorities will receive the protocol, amendments, reports on SAEs, and the Integrated Clinical Trial Report according to national regulations. As required by local legislation, written approval will be obtained from the Regulatory Authorities prior to commencement of the trial and implementation of e.g. amendments as applicable.

11.4. Informed Consent

Written informed consent will be obtained from all subjects (or legally acceptable representative) before any trial-related procedures (including any screening or pre-treatment procedures) are performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The investigators have both ethical and legal responsibility to ensure that each subject being considered for inclusion in this trial is given a full explanation of the protocol. This shall be documented on a written informed consent form that shall be approved by the same IEC/IRB responsible for approval of this protocol. Each

informed consent form shall include the elements required by the international GCP and must adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or qualified designees) and it is felt that the subject understands the implications of participating, the IEC/IRB approved written informed consent form will be signed and dated by both the subject and the person obtaining consent (investigators or designees), and by any other parties required by the IEC/IRB.

The original signed informed consent form will be kept with the trial records and a copy of signed informed consent form will be provided to the subject. Another copy of the signed informed consent form and a source document identifying the trial and recording the dates of participation will be placed in the subject's medical record.

The monitor will inspect the original completed consent form(s) for all subjects.

11.5. Confidentiality

All site staff, the sponsor, and any sponsor representatives will preserve the confidentiality of all subjects taking part in the trial, in accordance with International GCP, applicable local legislation/regulations. Subject to the requirement for source data verification by the trial personnel by reference to the subject's notes, confidentiality of all subject identities will be maintained. Only subject trial number and initials will be used on the CRF and in all trial correspondence, as permitted. No material bearing a subject's name will be kept on file by the sponsor. The written informed consent will contain a clause granting permission for review of the subjects' source data.

12. 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 the sponsor shall not be published or disclosed to a third party, other than to the responsible IEC/IRB, within the understanding of the confidentiality of their nature, without the prior written consent of the sponsor.

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 sponsor and investigator(s), including site clinical and laboratory investigators, as appropriate.

13. PROTOCOL AMENDMENT POLICY

Any change to the protocol will be effected by means of a protocol amendment. Any changes which affect subject safety or welfare will be submitted to the IEC/IRB and Regulatory Authorities prior to implementation. The investigator, IEC/IRB, and sponsor must agree on all amendments. No amendment will be implemented until approved by the relevant Authorities and/or IEC/IRB and signed by all required parties. Exceptions to this are when the investigator considers that the subject's safety is compromised.

Protocol amendments detailing minor administrative changes should be submitted by the investigator to the IEC/IRB and Regulatory Authorities, either for notification purposes or approval as appropriate.

14. FINANCIAL ASPECTS, INSURANCE AND INDEMNITY

The trial sponsor is the Global Alliance for TB Drug Development (TB Alliance). The 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 antiretroviral therapies for those HIV-TB subjects currently on such therapies, and improve treatment of latent infection.

The 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.

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

The subjects will not receive any incentive for their involvement in the trial. The sponsor has made provision to reimburse the subjects 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.

The sponsor 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. The sponsor does not assume any obligation for the medical treatment of other injuries and illnesses.

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Appendix 1: THE IUATLD SCALE

The IUATLD scale proposes five groups for reporting the results of reading smears for acid fast bacilli. They should be recorded as follows:

FINDING	RECORDING
No acid-fast bacilli found in at least 100 fields	negative
1 to 9 acid-fast bacilli per 100 fields	scanty positive
10 to 99 acid-fast bacilli per 100 fields	+
1 to 10 acid-fast bacilli per field in at least 50 fields	++
More than 10 acid-fast bacilli 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.

Appendix 2: 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 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

Ref: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109.

Appendix 3: 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 diarrhea for >1 month • Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) • Persistent oral candidiasis (thrush) • Oral hairy leukoplakia • Pulmonary tuberculosis (current) • Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) • Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis • Unexplained anemia (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 tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Cryptococcosis, extrapulmonary (including meningitis) • Disseminated nontuberculosis mycobacteria infection • Progressive multifocal leukoencephalopathy • Candida of the trachea, bronchi, or lungs • Chronic cryptosporidiosis (with diarrhea) • 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*

Appendix 4: DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE

Source: U.S. National Institute of Allergy and Infectious Diseases, DMID, November 2007 (Draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

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	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of subjects in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 /mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent ; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient - no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25- 50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Appendix 5: COCKCROFT-GAULT FORMULA

1. Ensure that the creatinine is expressed in µmol/L
    a. If your lab reports the creatinine in mg/dL : multiply by 88.4
    b. If your lab reports the creatinine value in µmol/L : use this value

2. Calculate the creatinine clearance using the Cockcroft-Gault formula

$$\text{Creatinine Clearance} = \frac{(140 - \text{Age}) \times \text{Weight (in kilograms)} \times \text{Constant}}{\text{Serum Creatinine (in µmol/L)}}$$

Where Constant is 1.23 for men and 1.04 for women.

Appendix 6: MALARIA GUIDELINES

Recommendations for trial NC-006-(M-Pa-Z), During Treatment Period

Medication	Guideline
Quinine	Stop trial medication. Balance need of prompt start of antimalarial treatment vs. risk of QTc prolongation.
Chloroquine	Stop M-Pa-Z trial medication. Balance need of prompt start of antimalarial treatment vs. risk of QTc prolongation.
Amiodaquine	Stop trial medication. Balance need of prompt start of antimalarial treatment vs. risk of QTc prolongation.
Mefloquine	Stop trial medication. Balance need of prompt start of antimalarial treatment vs. risk of QTc prolongation.
Halofrantine	Stop trial medication. Balance need of prompt start of antimalarial treatment vs. risk of QTc prolongation.
Lumefrantine	Stop trial medication. Balance need of prompt start of antimalarial treatment vs. risk of QTc prolongation.
Primaquine	Consider continuing trial medication depending on clinical judgment.
Pyrimethamine	Consider continuing trial medication depending on clinical judgment.
Proguanil/Atovaquone	Consider continuing trial medication depending on clinical judgment. Keep in mind that rifampicin (HRZE treatment) reduces the serum concentration of Proguanil/Atovaquone (Malarone) by ~ 50%.
Artemisin	Consider continuing trial medication depending on clinical judgment.

Selected characteristics of anti-malarial compounds and trial medications.

Compound	Half Life	Prolongation of QT interval (oral administration)	Interactions (Note: this is not and exhaustive list)
Quinine	12-18 hours	+	QT prolonging agents: Use caution with medications which may prolong the QT interval or cause cardiac arrhythmias. Antihypertensives, Phenothiazines, Codeine, Cardiac Glycosides (e.g.digoxin)
Artemisin	2-5 hours	0	Artesunate (Artemisin derivative) dosages need not be changed because of hepatic or renal failure or concomitant or previous therapy with other medications, including previous therapy with mefloquine, quinine or quinidine. There are no known interactions between artesunate and other drugs.

Appendix 7: TB SYMPTOMS PROFILE

TUBERCULOSIS SYMPTOM PROFILE (V3)

This questionnaire asks about symptoms that patients with tuberculosis may or may not experience.

Please read each symptom carefully and think about your experience **during the past 7 days** when you make your response. Then tick (☑) one box for each symptom.

If you **did not** experience the symptom **during the past 7 days**, please tick (☑) "None" for that symptom.

If you **did** experience the symptom **during the past 7 days**, please tick (☑) whether the intensity of the symptom you experienced was "Mild", "Moderate" or "Severe".

TB Symptom	Rate your experience of each symptom over the past 7 days.			
Feeling feverish	☐ None	☐ Mild	☐ Moderate	☐ Severe
Feeling chills	☐ None	☐ Mild	☐ Moderate	☐ Severe
Excessive sweating	☐ None	☐ Mild	☐ Moderate	☐ Severe
Shortness of breath	☐ None	☐ Mild	☐ Moderate	☐ Severe
Chest pain	☐ None	☐ Mild	☐ Moderate	☐ Severe
Feeling unwell	☐ None	☐ Mild	☐ Moderate	☐ Severe
Tiredness/weakness	☐ None	☐ Mild	☐ Moderate	☐ Severe
Cough	☐ None	☐ Mild	☐ Moderate	☐ Severe
Coughing up mucus	☐ None	☐ Mild	☐ Moderate	☐ Severe
Coughing up blood	☐ None	☐ Mild	☐ Moderate	☐ Severe

During the past 7 days, how would you rate your appetite?

☐ Good ☐ Fair ☐ Poor

Approved, Issued Date 09-Apr-2012

Appendix 8: PATIENT REPORTED HEALTH STATUS QUESTIONNAIRE

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

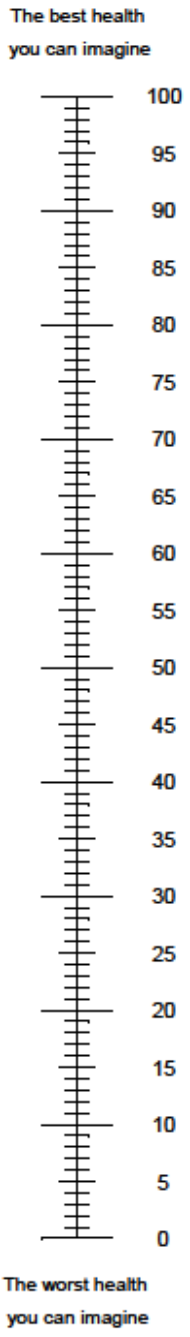
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

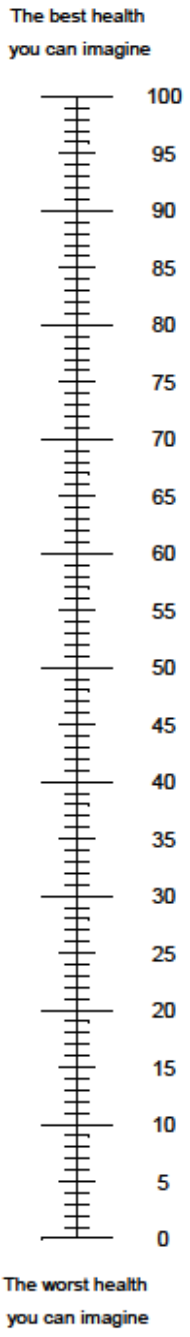
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 9: LIVER TOXICITY MANAGEMENT

Standard anti-TB chemotherapy is known to cause derangement of liver function tests in a substantial number of patients. In many cases this will be asymptomatic and self-limiting. In some cases severe hepatitis and even fulminant liver failure and death can occur.

In pre-marketing clinical trials of new drugs and regimens it is especially important to identify and carefully manage any trial subjects who are at risk of progression to serious liver injury. The observation of altered liver function to a degree that has a high risk of progressing to liver failure has been referred to informally as *Hy's Law* (Temple 2001; Reuben 2004); this reflects that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
2. Among trial subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum total bilirubin (TBL) to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury

During the trial, liver function will be monitored regularly with clinical assessment and blood tests in study participants and this will assist in follow up laboratory measurements that can document either resolution of abnormalities or signal the potential for drug-induced liver injury (DILI). In a clinical trial of new drugs and combinations it is especially important for investigators to follow closely any subjects who have evidence of hepatic inflammation or potential toxicity. The following procedure describes the management of deranged liver function tests in study participants.

Procedure

Blood tests for liver function will be taken routinely at screening (Day -9 to -1) and at the specific time points designated in the protocol, and at Early Withdrawal. If at any other visit the clinician suspects derangement of liver function, e.g. the subject describes nausea and vomiting, right upper abdominal pain or is jaundiced, blood should be taken for liver function tests and the subject comprehensively assessed for evidence of hepatitis or hepatic impairment and any potentially contributing causes.

The laboratory source (print-out of any results) should be stored alongside or transcribed into the clinical source document. Each abnormal value should be marked as clinically significant (CS) or non-clinically significant (NCS); the assessment of significance is at the discretion of the investigator. All clinically significant abnormal results must be recorded as Adverse Events in the e CRF and graded clinically as per the DMID adult toxicity **table** grading (**Error! Reference source not found.**). Assessments and decision making for elevations in aminotransferase values or bilirubin of various levels of concern are detailed below:

Decision to Consider Stopping Drug Regimen Administration

Consideration of stopping drug administration, at least temporarily, to subjects with liver function abnormalities or signs and symptoms of hepatitis should be discussed with the sponsor medical monitor, especially in the following situations:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

The drug regimen should be interrupted and the subject's clinical course should be discussed with the sponsor medical monitor in the following situation:

- ALT or AST >3xULN **and** Total Bilirubin >2xULN

More detailed assessments and decision making for elevations in aminotransferase values or bilirubin of various levels of concern are detailed below:

Grade 3 (DMID grading: ALT, AST, AP greater than or equal to 3X ULN to 8ULN if a substantial increase from baseline (such as > 2-fold increase):

Contact the subject and recall them as soon as possible. Assess the subject for other signs and symptoms of more specific hepatic events including hepatic impairment and or hepatitis. If you are concerned you should consider arranging for the subject to present to a medical facility (e.g. emergency department) immediately for assessment.

- Assess the clinical significance –the subject has jaundice, a coagulation disorder or signs of hepatic encephalopathy. All study drugs should be withheld pending assessment/improvement.
- Assess possible contributing factors – This should include (but is not limited to) alcohol, intra-venous and other drug use, travel, unwell contacts, any medications with known hepatotoxic potential, herbal products and dietary supplements, previous or known hepatitis infection and exposure to environmental chemical agents. Although anti-TB chemotherapy is known to cause liver function test derangement, the subject should always be assessed for other possible causes or contributing factors.
- The subject should also be advised to stop taking any medications/substances, other than the study medications to treat TB, that may be contributing to or causing derangement of liver function tests.
- Make every effort to repeat the testing of ALT, AST, AP and bilirubin within 48-72 hours to confirm the abnormalities and to determine if they are increasing or decreasing. Consider any additional laboratory tests that may help characterize the subject's clinical condition. Subjects should have tests for causes of viral hepatitis (e.g. hepatitis A and B and any other tests available of viral hepatitis). If tests for viral hepatitis are not available or not done it may still be helpful to collect an additional 10ml sample for serum for freezing (5ml yellow/SST tube x2) which may be tested later. The subject's consent must be obtained for this.

Elevated liver enzymes considered of clinical significance, but not accompanied by other signs and symptoms, should be reported as an adverse event and should usually be recorded as elevated liver enzymes. If the term "hepatitis" is used, the Safety Data Manager will question the site for additional evidence to support the diagnosis, such as clinical signs and serological or biopsy data. While a liver biopsy is not required to make a diagnosis of hepatitis, the term "hepatitis" should be reserved in most instances for cases where there is supportive evidence beyond a liver enzyme abnormality. However, if the investigator will confirm the diagnosis of hepatitis just on the basis of clinical signs and laboratory values the diagnosis will be accepted. Should other symptoms or signs be present, these should also be recorded as adverse events.

If liver function tests are Grade 4 (DMID grading: ALT, AST, AP > 8 ULN:

- Contact the subject and recall them as soon as possible. Generally the clinical trial medication should be withdrawn, but this should be discussed first with the sponsor Medical Monitor whenever possible. Assess the subject for other signs and symptoms of more specific hepatic events including hepatic impairment and or hepatitis. If you are concerned you should consider arranging for the subject to present to a medical facility (e.g. emergency department) immediately for assessment.

- Assess the clinical significance – Consider hospitalisation if the ALT is more than 10 times the ULN and/or the subject has jaundice, a coagulation disorder or signs of hepatic encephalopathy. All study drugs should be withheld pending assessment/improvement.
- Assess possible contributing factors – This should include (but is not limited to) alcohol, intra-venous and other drug use, travel, unwell contacts, any medications with known hepatotoxic potential, herbal products and dietary supplements, previous or known hepatitis infection and exposure to environmental chemical agents. Although anti-TB chemotherapy is known to cause liver function test derangement, the subject should always be assessed for other possible causes or contributing factors.
- Make every effort to repeat the testing of ALT, AST, AP and bilirubin within 48-72 hours to confirm the abnormalities and to determine if they are increasing or decreasing. Consider any additional laboratory tests that may help characterize the subject's clinical condition. Subjects should have tests for causes of viral hepatitis (e.g. hepatitis A and B and any other tests available of viral hepatitis). If tests for viral hepatitis are not available or not done it may still be helpful to collect an additional 10ml sample for serum for freezing (5ml yellow/SST tube x2) which may be tested later. The subject's consent must be obtained for this.

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General principles for following subjects with potential liver toxicity

The subject should be contacted regularly depending on the Grade of Liver Function Test elevations and the magnitude of increase relative to baseline values for the subject. Initially this should be daily and subsequently depends on clinical course/individual circumstances. Staff must ensure that all subjects know to seek medical attention urgently if they experience any evidence of worsening liver disease. Symptoms may include (but are not limited to) malaise, fever, nausea, vomiting, loss of appetite, dark urine, yellowing of the eyes or skin (jaundice).

Liver function tests should be repeated regularly, such as every 3 days for the first week then once a week until they return to near baseline values for the subject. Manage the subject symptomatically as required using medications that are not potentially hepatotoxic. Infection control issues must be carefully managed whilst TB medications are being withheld, especially if the subject is still culture positive for acid fast bacilli.

Restarting medication

If the investigator, after consultation with the sponsor medical monitor, stops administration of the study medication, consideration may be given to re-starting the study medication. Once the liver function values have decreased substantially and any symptoms have significantly improved a decision must be made about further TB management. This will be dependent on the clinical context and a decision must be made in discussion with the sponsor medical monitor. In all cases treatment should be recommenced under close supervision for any evidence of recurrent liver function abnormalities.

If there is a further significant elevation of hepatic enzymes or bilirubin or symptoms of clinical concern after resumption of study medication, the study medication should be withdrawn permanently. Subjects who permanently discontinue study medication should be managed as clinically indicated according to local National TB Programme guidelines. The sponsor medical monitor can provide advice and examples of suitable treatment regimens to use if required.

Appendix 10: CARDIOVASCULAR SAFETY

ECG

All important abnormalities from the ECG readings will be reported.

The percentage of patients with increases in QTc of <30, 30-60, or > 60 ms from baseline will also be tabulated at each time point.

Abnormality Code	ECG parameter			
	HR	PR	QRS	$QT_{corrected}$
Abnormalities on actual values				
"Abnormally low"	≤ 50 bpm	NAP	≤ 50 ms	-
"Abnormally high"	≥ 120 bpm	≥ 210 ms	≥ 120 ms	-
"]450 ms, 480 ms]	-	-	-	450 ms < QTc ≤ 480 ms
"]480 ms, 500 ms]	-	-	-	480 ms < QTc ≤ 500 ms
"More than 500 ms	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline				
"[30; 60] ms"	-	-	-	[30; 60] ms
"> 60 ms"	-	-	-	> 60 ms

Vital Signs

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs parameter		
	Pulse	DBP	SBP
Abnormalities on actual values			
"Abnormally low"	≤ 50 bpm	≤ 50 mmHg	≤ 90 mm Hg
"Grade 1 or mild"	-	> 90 mmHg-<100 mmHg	> 140 mmHg-<160 mmHg
"Grade 2 or moderate"	-	≥ 100 mmHg-<110 mmHg	≥ 160 mmHg-<180 mmHg
"Grade 3 or severe"	-	≥ 110 mmHg	≥ 180 mmHg
"Abnormally high"	≥ 120 bpm	-	-