TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

CONFIDENTIAL

PROTOCOL

Protocol Title: A Phase 2 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of combinations of bedaquiline, moxifloxacin, PA-824 and pyrazinamide during 8 weeks of treatment in Adult Subjects with Newly Diagnosed Drug-Sensitive or Multi Drug-Resistant, Smear-Positive Pulmonary Tuberculosis.

Protocol Number: NC-005-(J-M-Pa-Z)

Working Protocol Version: 1.1 (Final)

Working Protocol Date: 19 September 2014

COMBINATION OF THE FOLLOWING APPROVED FINAL DOCUMENTS:

Protocol V1.0 dated 31 January 2014

Protocol Amendment 01 dated 19 September 2014

PROTOCOL SIGNATURE PAGE

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Working Protocol Version: 1.1 (Final)

Protocol Date: 19 September 2014

SPONSOR

I agree to the terms of this study protocol.

Signature of Senior Medical Officer

Stephen Murray
Printed Name

19 Sept 2014
Date

CO-ORDINATING INVESTIGATOR

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein and in accordance to the principals of Good Clinical Practice and local regulations.

Signature

RODNEY DAWSON
Printed Name

23 SEPT 2014
Date

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

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Protocol Number: NC-005-(J-M-Pa-Z)

Working Protocol Version: 1.1 (Draft)

Protocol Date: 19 September 2014

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:	2
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AREDS2	Age Related Eye Disease Study 2
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration time curve
$AUC_{(0-24)}$	Area under the plasma concentration time curve from zero to end of dosing interval
$AUC_{(0-t)}$	Area under the PK plasma concentration time (t) curve from zero to the last quantifiable PK plasma concentration prior to the subsequent dose, using the linear trapezoidal rule
BA	Bactericidal Activity
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood urea nitrogen
C	Clofazimine
°C	Degrees Celsius
CFU	Colony Forming Units
CK	Creatine Phosphokinase
CK-MB	Creatine Phosphokinase of Muscle Brain
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration at the end of the dosing interval
CNS	Central Nervous System
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interactions
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic acid
DOTS	Directly Observed Treatment, Short Course, Internationally agreed strategy for TB control
DS	Drug-Sensitive
DSMC	Data Safety Monitoring Committee
DST	Drug Sensitivity Testing
eCRF	Electronic Case Report Form
EBA	Early Bactericidal Activity
ECG	Electrocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
ERPF	Effective Renal Plasma Flow
FDA	United States Food and Drug Administration
FF	Filtration Fraction
FSH	Follicle-Stimulating Hormone

GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyltransferase
hERG	Human ether-à-go-go-related gene
HIV	Human Immunodeficiency Virus
hr	Hour
HRZE	isoniazid plus rifampicin plus pyrazinamide plus ethambutol
HRZM	Isoniazid plus rifampicin plus pyrazinamide plus moxifloxacin
IB	Investigator Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IUATLD	International Union Against Tuberculosis and Lung Disease
i.v	Intravenous
J	Bedaquiline (TMC207)
Kg	Kilogram
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
lKr	Delayed rectifier potassium current
LH	Luteinizing Hormone
LSLV	Last Subject Last Visit
m	Meters
M	Moxifloxacin
MBD	Minimum Bactericidal Dose
M2	Bedaquiline metabolite M2
MDR	Multi Drug-Resistant
MED	Minimum Effective Dose
mg	Milligrams
mg/dl	milligram per deciliter
MGIT	Mycobacterial Growth Indicator Tube
MIC	Minimum inhibitory concentration
ml	Milliliter
mmHg	Millimeter of mercury
M. Tb	*Mycobacterium Tuberculosis*
ms	Millisecond
NIH	National Institute of Health
NLME	Non-linear Mixed Effect
NOAEL	No Observed Adverse Effect Level
NRTI	Nucleoside Reverse Transcriptase Inhibitor
Pa	PA-824
PD	Pharmacodynamic
PE	Physical Examination

PK	Pharmacokinetic
PR	Electrocardiographic PR interval
q.d.	Once daily dosage
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
RR	Electrocardiographic RR interval
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sc	Subcutaneous
SIRE	Streptomycin, isoniazid, rifampicin and ethambutol
SSCC	Serial Sputum Colony Counts
T	Time
$t_{½}$	Apparent terminal elimination phase half-life
TB	Tuberculosis
TEAEs	Treatment-Emergent Adverse Events
t.i.w	Three times a week
T_{max}	Time at which C_{max} is observed
TMIC	Time over Minimum Inhibitory Concentrations
TTP	Time to Sputum Culture Positivity
UA	Uric Acid
ULN	Upper Limit of Normal
*u*g/ml	microgram per milliliter
WBC	White Blood Cell
WHO	World Health Organization
XDR	Extensively drug-resistant
Z	Pyrazinamide

Definitions:

BA (Bactericidal Activity)	An agent's ability to kill mycobacteria originating within pulmonary cavities.
BA_{TTP}	Determination of BA by measurement in an automated liquid culture system of time to positivity (TTP) of *M. Tuberculosis* from an Overnight Sputum Sample.
BA_{CFU}	Determination of BA by quantification of solid medium of viable Colony Forming Units (CFU) of *M. Tuberculosis* from an Overnight Sputum Sample.
pncA	pncA is a gene encoding pyrazinamidase in Mycobacterium species.

1. PROTOCOL SYNOPSIS

1.1. Synopsis

Name of Sponsor/Company:	Global Alliance for TB Drug Development	For National Authority Use Only
Name of Finished Products:	Bedaquiline tablets (J), Moxifloxacin tablets (M), PA-824 tablets (Pa), Pyrazinamide tablets (Z) and HRZE tablets.	
Protocol Title:	A Phase 2 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of combinations of bedaquiline, moxifloxacin, PA-824 and pyrazinamide during 8 weeks of treatment in Adult Subjects with Newly Diagnosed Drug-Sensitive or Multi Drug-Resistant, Smear-Positive Pulmonary Tuberculosis.	
Treatment Indication:	Pulmonary Tuberculosis (TB)	
Trial Objective:	Assess the mycobactericidal activity of combinations of bedaquiline, moxifloxacin, PA-824 and pyrazinamide regimens during 8 weeks of treatment.	
Trial Design:	Phase 2, multi-center, open-label, partially randomized clinical trial in four parallel treatment groups. Subjects with **Drug-Sensitive (DS) TB** will be randomized to receive either $J_{(\text{loading dose/t.i.w.})}$PaZ; or $J_{(200mg)}$PaZ; or HRZE. Subjects with **Multi Drug-Resistant (MDR) TB** will receive $J_{(200mg)}$MPaZ. The HRZE treatment arm is included as a control for the drug-sensitive treatments and as a control for the quantitative laboratory mycobacteriology testing. All Subjects will have up to a maximum of 9 days screening, receive 8 weeks of treatment, and have follow-up visits at 2 and 12 weeks after study treatment completion or last dose of IMP in the case of early withdrawal. Telephonic contact to collect survival data will be conducted at 6, 12, 18 and 24 months after completion of study treatment. Subjects who withdraw from the study after receiving $\leq$ 14 days of IMP, will only attend a follow-up visit at 2 weeks after the last dose of IMP and the telephonic contact will not be conducted for these Subjects, while Subjects completing > 14 days of treatment are required to complete all scheduled Follow Up. Upon treatment completion, the DS-TB Subjects will be provided with sufficient doses of standard of care TB treatment, as appropriate, to cover the time period from attending their last visit at the study clinic until their scheduled visit at the TB clinic. All DS-TB and MDR-TB Subjects will be referred to the local community TB clinics for standard anti-tuberculosis chemotherapy according to National TB Guidelines.	
Patient Population:	A total of approximately 240 male and female, newly diagnosed Subjects with drug-sensitive or multi drug-resistant, smear positive pulmonary tuberculosis aged 18 to 75 years (inclusive). A total of 180 DS-TB Subjects (60 per treatment arm) will be randomized. Up to 60 MDR-TB Subjects will be assigned.	
Test Product, Dose and Mode of Administration:	The Test Product will be supplied as: • Bedaquiline 100mg Tablets; • Moxifloxacin 400mg Tablets; • PA-824 200mg Tablets; • Pyrazinamide 500mg Tablets Treatment will be administered orally for 8 consecutive weeks (56 days), in the following dosing schemes: Subjects with **DS-TB**: • $J_{(\text{loading dose/t.i.w.})}$PaZ: Bedaquiline 400mg once daily Days 1-14, 200mg three times per week Days 15-56; plus PA-824 200mg once daily Days 1-56; plus pyrazinamide 1500mg once daily Days 1-56; • $J_{(200mg)}$PaZ: Bedaquiline 200mg once daily Days 1-56; plus PA-824 200mg once daily Days 1-56; plus pyrazinamide 1500mg once daily Days 1-56;	

	Subjects with **MDR-TB**: • $J_{(200mg)}$MPaZ: Bedaquiline 200mg once daily Days 1-56; plus moxifloxacin 400mg once daily Days 1-56; plus PA-824 200mg once daily Days 1-56; plus pyrazinamide 1500mg once daily Days 1-56. Instructions for Dosing of above IMP: • Preferably to be taken around breakfast time, with a glass of water (approximately 240ml); • Subjects <u>should take the above IMP with a meal</u> (generally allow the Subjects a window of 30 minutes before to 30 minutes after a meal); • **For the $J_{(loading\ dose/t.i.w.)}$ DS-TB treatment arm:** The bedaquiline dosing schedule is 400mg daily on days 1-14, and then 200mg 3x per week for Days 15-56. The 3x per week doses must be given on the following specific days to accommodate the PK sampling: Days 15, 17, 20, 22, 24, 27, 29, 31, 34, 36, 38, 41, 43, 45, 48, 50, 53 and 56.
Positive Control Product, Dose, and Mode of Administration:	The Control Product will be supplied as: • HRZE tablets (Isoniazid 75mg plus rifampicin 150mg plus pyrazinamide 400mg plus ethambutol 275mg combination tablets). Vitamin B6 25mg will be provided, prescribed and dispensed as a daily supplement to all Subjects participating in the HRZE treatment arm. Treatment will be administered orally once daily for 8 consecutive weeks (56 days) to DS-TB Subjects only, as follows: • HRZE tablets Days 1-56 with the daily dose per the Subject's weight as follows: 30-37kg: 2 tablets; 38-54kg: 3 tablets; 55-70kg: 4 tablets; 71kg and over: 5 tablets. • Vitamin B6: one 25mg tablet daily Days 1-56. Instructions for Dosing of above IMP: • Preferably to be taken around breakfast time, with a glass of water (approximately 240ml); • HRZE <u>should not be taken with a meal</u> (generally, no closer to meals than 1 hour before or 2 hours after a meal); • Vitamin B6 25mg supplement to be taken with the HRZE dose.

Criteria for evaluation:

- The Overnight Sputum Samples will be used to determine the primary outcome of the study.

<u>Primary Endpoint:</u> The Bactericidal Activity (BA_{TTP}(0-56)) as determined by the rate of change in time to sputum culture positivity (TTP) over 8 weeks of treatment in the Mycobacterial Growth Indicator Tube system, represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time.

<u>Secondary Endpoints</u>:

<u>Efficacy</u>:

- The BA_{TTP}(0-2) and BA_{TTP}(14-56) as determined by the rate of change in time to sputum culture positivity (TTP) over Days 0 to 2, and Days 14 to 56 treatment, represented by the model-fitted log(TTP) as calculated by the regression of the observed log(TTP) counts over time.
- The BA_{CFU}(0-56), BA_{CFU}(0-2) and BA_{CFU}(14-56) as determined by the rate of change in colony forming units (CFU) over 8 weeks of treatment, represented by the model-fitted log(CFU) results as calculated by the regression of the observed log(CFU) results over time.
- Time to sputum culture conversion using data from weekly cultures through 8 weeks of treatment (separately, on solid and liquid media).
- Proportion of Subjects with sputum culture conversion at 4, 6 and 8 weeks (separately, on solid and liquid media).
- The BA_{CFU}(0-56, 0-2 and 14-56) and BA_{TTP}(0-56, 0-2 and 14-56) of $J_{(loading\ dose/t.i.w.)}$PaZ compared to $J_{(200mg)}$PaZ from DS-TB treatment arms.

- Investigation of the methodology of sputum sampling by comparing CFU counts and TTP results, each quantified in both Coached Spot Sputum and Overnight Sputum samples; however Overnight Sputum Samples are considered the reference samples.

Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) will be presented by severity (DMID Grade), drug relatedness and seriousness, leading to early withdrawal and leading to death, by group.
- Quantitative and qualitative clinical laboratory result measurements, including observed and change from baseline will be presented and summarized by group.
- 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 also be categorized and presented, by group.
- Descriptive statistics will be presented for ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2] lens opacity classification and grading) and listed by Subject. Categorical data for lens opacity will be summarized in a frequency table for the left and right eye, respectively, including change from baseline, and summarized by group.
- Descriptive statistics will be presented for serum FSH measurements (mean and median at baseline, 4, 8, and 10 weeks and mean change from baseline at 4, 8, and 10 weeks) by group.
- Other safety variables will be presented by group and listed by Subject.

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

Pharmacokinetics:

Pharmacokinetics will consist of two separate schedules:

- *All Subjects:*

  Pre-dose sampling at Days 1, 4, 8, 15, 22, 29, 36, 43, 50 and during the site visit on Days 57 and 70 to measure C_{trough} levels of J, J metabolite M2, M, Pa and Z as per the table below.

- *PK Sub-study Subjects:*

  In addition to the general PK samples, there will be intense PK sampling on Days 14 and 56 at pre-dose, 1, 2, 4, 8 and 24 hours after dosing in a sub-group of 15 Subjects in each treatment arm across selected sites.

Pharmacokinetic Analysis:

All measured PK concentrations will be listed.

For the C_{trough} samples, only descriptive statistics will be prepared (average C_{trough}) derived for each analyte on Days 4, 8, 15, 22, 29, 36, 43, 50, 57 and 70 as follows:

Treatment Arm	Analyte/s	Subject Population
$J_{(loading\ dose/t.i.w.)}$PaZ	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}$PaZ	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}$MPaZ	J, J metabolite M2, M, Pa, Z	MDR-TB
HRZE	Z	DS-TB

For the PK sub-study samples, the following PK parameters will be estimated from the individual (per Subject) PK plasma concentrations: minimum observed PK plasma concentration (C_{min}), maximum observed PK plasma concentration(C_{max}), time to reach C_{max} obtained without interpolation (T_{max}), area under the PK plasma concentration time (t) curve from zero to the last quantifiable PK plasma concentration prior to the subsequent dose, using the linear trapezoidal rule ($AUC_{(0\text{-}t)}$), area under the PK plasma concentration time (t) curve from zero to 24 hours ($AUC_{(0\text{-}24)}$). These will be derived for each analyte, on Days 14 and 56, as follows:

Treatment Arm	Analyte/s	Subject Population
$J_{(loading\ dose/t.i.w.)}PaZ$	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}PaZ$	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}MPaZ$	J, J metabolite M2, M, Pa, Z	MDR-TB
HRZE	Z	DS-TB

$J_{(200mg)}PaZ$ compared to $J_{(loading\ dose/t.i.w.)}PaZ$ and $J_{(200mg)}MPaZ$:

In order to compare the effects of the two J dosing schemes on bedaquiline exposure, the C_{max}, C_{min} and AUC of J and M2 will be compared using PK sub-study data from days 14 and 56 from the $J_{(loading\ dose/t.i.w)}PaZ$ and $J_{(200mg)}PaZ$ DS-TB arms. A secondary comparison of the PK parameters from the sub-study parameters of J and M2 between the $J_{(200mg)}PaZ$ DS-TB and $J_{(200mg)}MPaZ$ MDR-TB treatment arms will also be performed.

Another comparison of J and M2 exposure will be performed using the C_{trough} data from the $J_{(loading\ dose/t.i.w)}PaZ$ and $J_{(200mg)}PaZ$ DS-TB arms, with a secondary comparison between the $J_{(200mg)}PaZ$ DS-TB and $J_{(200mg)}MPaZ$ MDR-TB treatment arms.

Pharmacokinetics-Pharmacodynamics (PK-PD):

Pearson correlation coefficients will be reported for the correlation analysis of all relevant PK-PD and exploratory PK-PD endpoints.

Descriptive summary statistics for TMIC will be presented.

Exploratory PK-PD Endpoints:

- Correlations between C_{trough} plasma drug concentrations, efficacy and safety findings will be performed in an exploratory fashion.
- Comparison of TMIC (based on data from the PK sub-study parameters) for J between $J_{(loading\ dose/t.i.w.)}$, PaZ and $J_{(200mg)}PaZ$ in DS-TB arms.
- Correlations between plasma drug concentrations and efficacy and safety findings will be performed in an exploratory fashion, as follows:
  BA_{TTP}(0-56) and BA_{TTP}(14-56) versus the following PK variables (at Day 14 and Day 56) will be presented for J, Pa and M:
  - C_{max}
  - AUC(0-24)
  - Time over Minimum inhibitory concentration (TMIC) of J, Pa and M, both with and without taking protein binding shift into account.

Exploratory Endpoints:

- Sub-analysis of the primary and secondary efficacy endpoints of the MDR-TB pyrazinamide resistant Subjects compared to the MDR-TB sensitive Subjects.
- Sub-analysis of the primary and secondary efficacy endpoints of the H or R mono-resistant Subjects will be evaluated as separate sub-groups.

General Mycobacteriology:

Overnight Sputum and Coached Spot Sputum Samples will be obtained at all scheduled visits, except the Screening Visit when only a Coached Spot Sputum Sample will be collected. Sputum samples will not be collected at Early Withdrawal Visits. Cultures will be grown from all Overnight Sputum and Coached Spot Sputum Samples collected from Day -2 onwards. The Overnight Sputum Samples will be considered the reference samples.

The following mycobacteriology assays will be carried out:

Sample	Type	Assessments	Comments
Screening	Coached Spot Sputum Sample	• Direct microscopy for acid-fast bacilli • Molecular assay for identification of *M.* Tb and drug susceptibility (such as GeneXpert or MTBDR*plus*) to confirm the diagnosis of TB and distinguish between DS-TB and MDR-TB • Molecular test for fluoroquinolone resistance (such as MTBDR*sl*) for MDR-TB Subjects to establish susceptibility to moxifloxacin	All to be performed at the Trial Appointed Laboratory.
Baseline Overnight Sputum Samples named Day -2 and -1	Overnight Sputum Sample	• Direct microscopy for acid-fast bacilli • Molecular / antigen test to confirm *M. Tb* • Culture: MGIT and Solid Media (quantitative for CFU) • DST : SIRE, Z • MIC : J, Pa, M • DNA for pncA Sequencing	Z DST resistance must be repeated to confirm.
Baseline Coached Spot Sputum Samples named Day -2 and -1	Coached Spot Sputum Sample	• Culture: MGIT and Solid Media (quantitative for CFU)	For determination of logCFU and logTTP rates of change for comparison to cultures from Overnight Sputum Sample.
Overnight Sputum Sample named Days 1, 3, 7, 14, 21, 28, 35, 42, 49 and 56	Overnight Sputum Sample	• Culture: MGIT and Solid Media (quantitative for CFU) • The last positive sample from withdrawn Subjects who have not converted to culture negative status OR Subjects who are still culture positive at 8 weeks OR the first positive sample after conversion to culture negative status for subjects who have 'relapsed'***** o DST: SIRE, Z o MIC: J, Pa, M	
Coached Spot Sputum Sample named Days 1, 3, 7, 14, 21, 28, 35, 42, 49 and 56	Coached Spot Sputum Sample	• Culture: MGIT and Solid Media (quantitative for CFU)	For determination of logCFU and logTTP rates of change for comparison to cultures from Overnight Sputum Sample.

- The above assays will be carried out according to procedures described in the Laboratory Manual.
- The Coached Spot Sputum Sample can be used for all assays, except CFU and TTP, if results cannot be obtained from the Overnight Sputum Sample.
- pncA sequencing and MIC isolates can be batched at the end of the study.
- *****If the Subject was treated with study medication for less than 9 days, the mycobacteriology testing will be performed on the Day -2 sample isolate only.
- *****Culture negativity is defined as the first of two consecutive negative cultures, except for the week 8 time point, where a singular negative is acceptable.

Statistical Methods:

The primary efficacy analysis of the primary efficacy endpoint, i.e. BA_{TTP}(0-56), as determined by the rate of change in the log TTP in sputum over 8 weeks of treatment, will be analyzed using non-linear mixed effects (NLME) regression modeling. Sensitivity analyses may be performed using different model assumptions for the NLME regression model. Subgroup analyses, such as by site and human immunodeficiency virus (HIV) status, may be performed as exploratory analyses. The Statistical Analysis Plan (SAP) will be developed before the database is locked.

Trial Duration:

Estimated date of first Subject enrolled: Quarter 3, 2014
Estimated date of last Subject enrolled: Quarter 3, 2015
Estimated date of last Subject completed: Quarter 2, 2018

Duration of study: ~38 months (12 months enrolment period plus up to 9 days screening plus 8 week treatment period plus 24 month post-treatment follow-up). In the event of the DS-TB treatment arms being fully recruited (i.e. 60 Subjects in each of the three treatment arms) before the MDR-TB treatment arm has enrolled 60 Subjects, the Sponsor may elect to close the study for all treatment arms or close the DS-TB treatment arms and continue the study with MDR-TB recruitment while analysing the DS-TB data.

1.2. Trial Flow Chart – Screening Period to Day 140 Follow Up Visit

Period	Screening			Treatment													Follow Up	
Visit Day [a]	(-9 to -3)[b]	-2[b]	-1	1	4	8	14[h]	15	22	29	36	43	50	56[h]	57	Early Withdrawal[r]	70	140
Week		-1		1				2	3	4	5	6	7		8		10	20
Written Informed Consent	X																	
Inclusion/Exclusion	X			X														
Demography	X																	
Medical & Treatment History	X																	
12-Lead ECG[c]	X			X				X		X		X			X	X	X	
Laboratory Safety Tests[d]	X		X	X		X		X	X	X	X	X	X		X	X	X	
Urine Pregnancy Test[e]	X									X					X	X	X	X
HIV and CD4 Count[f]	X																	
Urine Drug Screen[g]	X																	
Karnofsky Score	X																	
TB Symptom Profile (TSP) Questionnaire[S]	X							X		X					X	X		
Pharmacokinetic Sampling[h]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chest X-ray[i]	X[i]	(X[i])	(X[i])															
Vital Signs[j]	X		X	X	X	X		X	X	X	X	X	X		X	X	X	
Physical Examination - full[k]	X			X											X	X		
Physical Examination – limited[k]					X	X		X	X	X	X	X	X				X	
Ophthalmology[l] Examination	X[l]	(X[l])	(X[l])															X[l]
Randomization/Treatment Assignment[m]			X[m]	X[m]														
IMP Administration[n]				X	X	X	X	X	X	X	X	X	X	X				
Overnight Sputum Sample[o] *Name of Sample (Day)*		X *-2*	X *-1*	X *1*	X *3*	X *7*		X *14*	X *21*	X *28*	X *35*	X *42*	X *49*		X *56*			
Coached Spot Sputum Samples[p] *Name of Sample (Day)*	X *Screen*	X *-2*	X *-1*	X *1*	X *3*	X *7*		X *14*	X *21*	X *28*	X *35*	X *42*	X *49*		X *56*			
Concomitant Meds/ Other Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Referral to National TB Treatment Program															X	X		

1.3 Trial Flow Chart – 8 to 26 Month Telephonic Survival Follow Up Period

Period	8 – 26 Month Telephonic Survival Follow Up Period			
Month	Month 8 (6 months after study treatment completion)	Month 14 (12 months after study treatment completion)	Month 20 (18 months after study treatment completion)	Month 26 (24 months after study treatment completion)
Obtain Subject survival data	x	x	x	x

a: **Visit Window periods:**
- Up to and including Day 15 - No visit window (in order to accommodate PK sampling);
- Day 14 must occur on Day 14, relative to Day 1 (in order to accommodate PK sampling for PK sub-study Subjects only);
- Days 22 to 50 +/- 2 days;
- Days 56 and 57 must occur on Days 56 and 57, relative to Day 1 (in order to accommodate PK sampling. The Day 56 visit is for PK sub-study Subjects only);
- Day 70 (or 2 weeks after last dose of IMP in the case of early withdrawal) +/- 3 days;
- Day 140 (or 12 weeks after last dose of IMP in the case of early withdrawal) +/- 14 days;
- The 8, 14, 20 and 26 Month Telephonic Survival Follow Up Contacts will be 6, 12, 18 and 24 months, respectively, after study treatment completion +/- 14 days;

  Please Note : IMP dosing should not exceed 56 days even if visit windows are utilized;
  : If a visit window is utilized, the next visit must be scheduled relative to Day 1.

b: **Screening Days -9 to -3:**
- May occur over a number of days i.e. all screening procedures do not have to be performed on the same day.

c: **12-lead ECGs:**
- Single ECG to be performed at Screening Visit, all other ECGs to be done in triplicate.
- All ECGs to be performed before any other assessments and before IMP administration.
- Results from central reading of Day -9 to -3 ECG should be used to determine eligibility.
- At Day 29 a triplicate ECG is performed both pre-dose and then again 2 hours (+/- 15 minutes) post IMP administration.

d: **Laboratory Assessments (refer to Section 6.3 for details of Laboratory Safety Assessments):**
- During the treatment period, safety laboratory samples to be collected prior to dosing. The Day-1 collection and testing is for Serum FSH only.
- Serum FSH performed at Baseline (Day -9 to -3 and Day-1), Days 29, 57 and 70 or at the Early Withdrawal Visit on male Subjects only.

e: **Urine Pregnancy Test:** Women of child bearing potential only, whether they are sexually active or not.

f: **HIV and CD4 Count:**
- If an HIV test was performed within 1 month prior to trial start, it need not be repeated as long as documentation can be provided (ELISA and/or Western Blot).
- For specific ART treatment allowed while the Subject is on IMP please refer to section 4.8.1.2
- Subjects may be on current ART or commence ART during the study if required, provided there is at least a 2 week interval between commencing IMP and the start of ART.

g: **Urine Drug Screen:** Cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, barbiturates.

h: **Pharmacokinetic Sampling:**

Pharmacokinetic Sampling will consist of two separate schedules:

- *All Subjects:*
  Pre-dose sampling at Days 1, 4, 8, 15, 22, 29, 36, 43, 50 and during the site visit on Days 57 and 70, to measure C_{trough} levels of J, J metabolite M2, M, Pa, Z.
- *PK Sub-study Subjects:*
  In Addition to the general PK samples, there will be intense PK sampling on Days 14 and 56 at pre-dose, 1, 2, 4, 8 and 24 hours after dosing in a sub-group of 15 Subjects in each of the treatment arms across selected sites.
- PK Sub-group Subjects do not need to be hospitalized for the PK sampling, but may remain as outpatients at the clinic for the applicable day, and return the following morning for their 24 hour post-dosing sample collection.
- PK samples are to be collected at the specified time points within the allowed applicable window periods as follows: Pre-dose: 0-5 minutes before dose; 1-8 hours post-dose: +/- 5 minutes of dosing time; 24 hours post-dose: +/- 15 minutes of dosing time and prior to next dose.
- The site staff should attempt to take the PK samples at the same time of day for each time point.

i: **Chest X-Ray:**

- May be performed at Day -2 or Day -1 if not already performed at Day -9 to -3; or if performed within 7 days prior to signing consent, the X-ray does not need to be repeated if the report and X-ray are available for review and interpretation.

j: **Vital Signs:**

- Systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg), heart rate (beats per minute [bpm]), respiratory rate (RR - breaths per minute), body temperature (^{0}C) and weight (kg).
- During the treatment period, to be performed before IMP administration.
- The same method for measurement of body temperature should be used throughout the study.

k: **Physical Examinations:**

- Height (m) will only be measured at Day -9 to -3.
- Limited Physical Examinations include: pulmonary, cardiovascular and abdominal examinations.
- During the treatment period, to be performed before IMP administration.

l: **Ophthalmology Examination:**

- Ophthalmologic medical history, visual acuity and slit lamp examination will be performed by an ophthalmologist with AREDS2 training during the screening period (Days -9 to -1), and at Day 140 or at least 90 days post the last dose of study medication. The study Ophthalmologist could delegate the Visual Acuity Test examination to a trained optometrist or other qualified personnel. The Ophthalmologists would still be responsible to review, approve and sign-off the Ophthalmology Report Forms, including sections completed by other designated personnel.
- May be performed at Day -2 or Day -1 if not already performed at Day -9 to -3.

m: **Randomization/Treatment Assignment:**

- Initial randomization may occur once all of the screening results are available and the Investigator has determined that the Subject is eligible for the trial.
- May occur at Day 1 if not already performed at Day -1.

n: **Investigational Medicinal Product (IMP) Administration:**

- To be taken orally once daily for 8 weeks (56 days), preferably around breakfast time, with a glass of water (approximately 240ml);
- Subjects on the HRZE treatment arm should not take IMP with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) and should take the Vitamin B6 25mg supplement with the HRZE dose;
- Subjects on the bedaquiline containing arms should take IMP with a meal (generally allow the Subjects a window of 30 minutes before to 30 minutes after a meal);
- When Subjects return for clinic visits or are hospitalized, they will be dosed on site;
- **For the $J_{(loading\ dose/t.i.w.)}$ DS-TB treatment arm:** The bedaquiline dosing schedule is 400mg daily on Days 1-14, and then 200mg 3x per week for Days 15-56. The 3x per week doses must be given on the following specific days to accommodate the PK sampling: Days 15, 17, 20, 22, 24, 27, 29, 31, 34, 36, 38, 41, 43, 45, 48, 50, 53 and 56.

o: **Overnight Sputum Sample (refer to Section 6.1 and 6.2 for details of procedures):**

- Overnight Sputum Sample may be collected for a number of screening days if the screening Spot Sputum Sample results are delayed, or the mycobacterial testing on the first Spot Sputum Sample shows an indeterminate result, in which case the test may be repeated on freshly collected Coached Spot Sputum or an Overnight Sputum Sample, and that result will be used.
- Of the screening period samples collected, only the Day -2 and Day -1 Overnight and Coached Spot Sputum samples will be used for the Efficacy Endpoint tests.
- ***Naming of Overnight Sputum Samples for the Trial Period Days -3 to Day 1:*** The day Overnight Sputum Sample collection **ends** reflects the day to which that sample applies e.g. a sample where collection starts on Day -3 and ends on Day -2, is designated as the Day -2 Overnight Sputum Sample and results are also referred to as Day -2 results.
- ***Naming of Overnight Sputum Samples for the Trial Period Days 3 to 57:*** The day Overnight Sputum Sample **starts** reflects the day to which that sample applies e.g. a sample where collection starts on Day 3 and ends on Day 4, is designated as the Day 3 Overnight Sputum Sample and results are also referred to as Day 3 results.
- The Subject should be instructed to collect the sample from approximately 4pm the afternoon prior to the visit and for approximately 16 hours overnight for each of the sampling days. Collection must be completed prior to the administration of the next day's IMP, which will be administered at the study site.
- If a Subject arrives at a clinic visit without an Overnight Sputum Sample or if no results could be obtained from the Overnight Sputum Sample, the Coached Spot Sputum Sample will be used for all assays.
- All isolates from positive cultures should be stored until study completion.

p: **Coached Spot Sputum Sample (refer to Section 6.1 and 6.2 for details of procedures):**

- If the Screening Spot Sputum smear or molecular testing shows a negative/scanty/indeterminate result, the test may be repeated on freshly collected Coached Spot Sputum Sample or Overnight Sputum Sample during the allocated screening period.
- In addition to using the Coached Spot Sputum Sample as comparator against the Overnight Sputum Sample for the rate of change in logCFU and logTTP, the Coached Spot Sputum Sample can also be used for all assays, except CFU and TTP, if results cannot be obtained from the Overnight Sputum Sample.
- ***Naming of Coached Spot Sputum Samples for the Trial Period Days -9 to Day 1:*** The Day -9 to -3 Coached Spot Sputum Sample/s will be named 'screen' (note, there is no matching Overnight Sputum Sample). The naming of Coached Spot Sputum Samples for Days -2, -1 and 1 will be designated as Day -2, -1 and 1 respectively and results are also referred to as Day -2, -1 and 1 results.
- ***Naming of Coached Spot Sputum Samples for the Trial Period Days 3 to 57:*** The naming of Coached Spot Sputum Samples will match the naming of Overnight Sputum Samples for that period, i.e. the Coached Spot Sputum Sample collected on Visit Day 4 will be named Day 3 etc. and results are referred to as Day 3 results.
- All isolates from positive cultures should be stored until study completion.

q: **Adverse events:** Will be collected by the Investigator from the time a Subject signs the Informed Consent Form until the Subject has completed their last follow-up visit as follows:

- All AEs and SAEs – through to the end of the Day 70 Visit;
- Only ophthalmologic related AEs and all SAEs - from Day 70 through to Day 140 Visit;
- Deaths reported during the Survival Follow Up period wil be reported as SAES.

r: **Early Withdrawal:**

- Subjects who withdraw after 14 days or less of IMP administration are to return for the first follow-up visit (i.e. 2 weeks after the last dose of IMP) only.
- Subjects who withdraw after $\geq$ 15 days of IMP administration are to return for the first and second follow-up visits (2 and 12 weeks after last dose of IMP). The 8, 14, 20 and 26 Month Telephonic Survival Follow Up Contact will also be carried out for these Subjects.

s: **Tuberculosis Symptom Profile (TSP) Questionnaire:**

- To be completed once during Visit Days -9 to -3, Day 15, Day 29, Day 57 and the Early Withdrawal Visit.

2. INTRODUCTION

2.1. Background

Although some progress has been made in recent years in controlling 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 fatal infectious diseases, and there is more TB in the world today than at any other time in history. The current first-line anti-tuberculosis agents have been in use for over 20 years and 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 compliance 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 compliance, drug resistance is becoming more common and fears of an epidemic with virtually untreatable strains of TB – extensively drug resistant TB (XDR-TB) - are growing. Since the discovery of the rifamycins [(1)], and their introduction into standard anti-tuberculosis regimens, very few new classes of drugs have been evaluated with a view to their registration as anti-tuberculosis agents.

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. On December 28, 2012 the U.S. Food and Drug Administration approved bedaquiline (Sirturo™) as part of combination therapy to treat adults with multi drug-resistant pulmonary tuberculosis (MDR-TB) when other alternatives are not available. In November of 2013, the CHMP recommended that delaminid be approved by the EMA for treatment of pulmonary MDR-TB in combination with the WHO optimized background regimen. Although both of these regulatory actions are positive steps, more work needs to be done to develop new regimens for both drug-sensitive (DS-TB) and MDR-TB. New combination regimens are desperately needed for two reasons; to shorten treatment to a duration more easily manageable by patients and public health services for DS-TB and to provide more efficacious, safer, better tolerated and affordable treatment for the growing number of patients suffering from MDR-TB and XDR-TB.

The bactericidal action of anti-tuberculosis agents alone or in combination can be quantified by studying the fall in the number of colony forming units (CFU) of M. tuberculosis (*M. Tb*) present in the sputum of clinical study Subjects with microscopy smear-positive pulmonary TB. In the first comprehensive evaluation of this technique all of the then available anti-tuberculosis agents were studied both alone and in combination during the first 14 days of treatment in small groups of approximately 4 Subjects [(2)]. This study showed significant differences between the different drugs, but these differences were most obvious during the first 2 days of treatment and this period of activity was consequently labeled EBA (for early bactericidal activity) or “standard EBA”. More recently, EBA studies have been conducted over 5, 7 and 14 days and it has become apparent that valuable additional information may be found by conducting EBA studies for longer than 2 days, including providing an indication of sterilizing as well as bactericidal activity, and dose-ranging information, in addition to safety, tolerability and PK data [(3-6)]. A review of EBA studies conducted on the key anti-tuberculosis drugs has shown the value these studies offer to demonstrate the early anti-tuberculosis effect that a new therapeutic agent may have and to explore the relationships between dose, pharmacokinetics and bactericidal activity in Subjects [(7).]

In the past five years, EBA methodology of quantitative colony counting on solid medium has been adapted to Phase 2b, 8-week TB treatment trials based on serial sputum colony counting to provide a more sensitive efficacy endpoint than the previously used binary endpoint of rate of sputum conversion measured after 8 weeks of treatment [(8-10)]. This type of trial, sometimes referred to in the literature as a serial sputum colony counting (SSCC) trial relies on performed throughout the treatment period, and a nonlinear mixed-effects approach to data analysis, to provide a more sensitive, continuous, surrogate measure indicative of a TB treatment’s efficacy over a two-month period. Such studies are conducted to provide data on which to base the selection of treatment-shortening regimens to be advanced into pivotal registration Phase 3 evaluation studies. The TB Alliance has recently completed one such study, NC-002, which investigated the efficacy and

safety of 2 months of treatment with PA-824 in combination with moxifloxacin and pyrazinamide in both DS-TB and MDR-TB. The study is still undergoing analysis, but preliminary results indicate that this combination demonstrates a greater rate of bacterial load reduction during the 8 weeks of treatment compared to the current isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) standard of care.

The current study (NC-005) is an "SSCC" 8 week trial designed to further the investigation and development of the combination of bedaquiline, PA-824 and pyrazinamide (J-Pa-Z) in DS-TB and bedaquiline, moxifloxacin, PA-824 and pyrazinamide in MDR-TB, following the successful demonstration that bedaquiline, PA-824 and pyrazinamide has good 14 day EBA activity in the recently-completed 14 day EBA Study NC-003.

2.2. Agents to be Studied

2.2.1. Bedaquiline

Bedaquiline (TMC207; Sirturo™ package insert [11]) is a new agent being developed for TB treatment. As detailed in the Investigator's Brochure [12,13] bedaquiline is a diarylquinoline that offers a novel mechanism of anti-tuberculosis action by specifically inhibiting mycobacterial adenosine triphosphate (ATP) synthase. [14] *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. Tb* isolates [15, 16], and is also bactericidal against non-replicating *M. Tb* [17]. In the murine model of TB, bedaquiline was as active as the triple combination of isoniazid (H), rifampin (R), and pyrazinamide (Z). Addition of bedaquiline to HRZ results in accelerated clearance of *M. Tb* [3, 4]. There appears to be a synergistic interaction with pyrazinamide: 100% of mice were culture negative after 8 weeks of treatment with bedaquiline and pyrazinamide compared to 0% of mice treated with the standard regimen of rifampicin, isoniazid and pyrazinamide [18]. Collectively, these findings in the mouse model have led to the suggestion that regimens containing bedaquiline and pyrazinamide could be effective in the treatment of both DS- and MDR-TB and shorten treatment duration in patients. While the combination of bedaquiline and PA-824 in the murine model of TB appeared somewhat antagonistic relative to bedaquiline alone, it was as active as the triple combination of HRZ [18] and in a subsequent study it was more active in the mouse model than HRZ [19]. Thus a novel regimen with a bedaquiline plus PA-824 core could be effective in the treatment of MDR-TB by providing two novel drugs for which there is no known pre-existing resistance.

To date, bedaquiline has been studied as monotherapy in two dose-ranging EBA trials (C202 and TMC207-CL001) [20,21], in two combination EBA trials (NC-001 [22] and NC-003) and in 2 Phase 2b studies (C208 and C209). In the monotherapy studies, bedaquiline was dosed over a range of 100-400 mg/day. Subjects with TB had approximately a 1 log decrease in logCFU over 14 days at all doses studied. The first 14 day EBA combination study (NC-001) demonstrated that bedaquiline in combination with pyrazinamide (J-Z) and bedaquiline in combination with PA-824 (J-Pa) had positive EBA activity. The second 14 day EBA combination study (NC-003), currently undergoing analysis, included a number of bedaquiline-containing arms: bedaquiline, pyrazinamide and clofazimine (J-Z-C), bedaquiline, PA-824 and clofazimine (J-Pa-C); bedaquiline, PA-824 and pyrazinamide (J-Pa-Z) and bedaquiline, PA-824, pyrazinamide and clofazimine (J-Pa-Z-C). Among these, J-Pa-Z had the best activity which was at least as good as the HRZE control. Finally, the 2 completed Phase 2b studies form the pivotal studies reviewed by the FDA for accelerated approval of bedaquiline (Sirturo™). Together, these clinical studies provide justification for proceeding to the current study and are described briefly below and in greater detail in the IB.

2.2.1.1. Bedaquiline Preclinical Studies

Full details of the preclinical studies are provided in the current bedaquiline Investigator's Brochure [12,13] and Sirturo ™ label [11]. *In vitro* studies have demonstrated that the range of minimum inhibitory concentrations (MICs) for *M. Tb* H37Rv, the international reference strain, and 6 fully drug-susceptible clinical isolates, was 0.030 to 0.120 µg/ml. The activity of bedaquiline appears to be specific for mycobacteria, as the MICs for non-mycobacteria were at least 500-fold higher. The activity of the main metabolite of bedaquiline, M2, was determined against *M. Tb* H37Rv in both solid and liquid media and its MIC was found to be 0.1 µg/ml. This MIC shows that M2 is active against *M. Tb* but 3-6 times less active than the parent compound bedaquiline.

Bedaquiline demonstrated similar *in vitro* efficacy against *M. Tb* clinical isolates resistant to the known anti-TB drugs (isoniazid, rifampin, pyrazinamide, streptomycin, ethambutol, or fluoroquinolones). As expected, from the lack of cross-resistance with currently used anti-tuberculosis agents, bedaquiline retained activity against MDR-TB isolates.

The non-clinical safety evaluation of bedaquiline includes pharmacology, pharmacokinetics, toxicology and metabolism studies that were conducted in accordance with current ICH guidelines. Repeated dose toxicity studies were performed with dosing durations up to 3 months in mice and up to 6 months in rats and in dogs. Recovery was studied in rats and dogs. In repeated dose toxicity studies up to 3 months in mice, up to 6 months in the rat and up to 9 months in dogs, bedaquiline was associated with target organ changes in the mononuclear phagocytic system (indicative of phospholipidosis), stomach, liver, pancreas, and muscle. Toxicity was often associated with an increased presence of neutrophils in some tissues such as the female genital tract and this was preceded by a peripheral neutrophilia. For more detailed information please refer to the bedaquiline IB [12,13].

Respiratory parameters in rats were unaffected by treatment. There were no effects suggestive of neurological impairment or delayed neurotoxicity in rats. In single dose toxicity studies there were no mortalities following oral doses of up to 200 mg/kg in mice and rats. No mutagenicity or clastogenic effects were seen in a series of *in vitro* and *in vivo* genotoxicity tests. Bedaquiline was evaluated for possible developmental toxicity effects in the rat and the rabbit. No teratogenic effects were found. *In vitro*, bedaquiline slightly to moderately inhibited the delayed rectifier potassium current (IKr) in the human ether-à-go-go-related gene (hERG) model. Bedaquiline and M2 had no notable effects on IKr at 0.01 µM (0.006 and 0.005 µg/mL, respectively). However, at higher concentrations (0.03 to 3 µM), both compounds had a slight to strong concentration-dependent effect with a 50% inhibitory concentration (IC_{50}) of 0.37 µM (0.2 µg/mL) for bedaquiline and up to 0.45 µM (0.24 µg/mL) for M2. However, this effect was not manifest as a prolongation of repolarization in subsequent *in vivo* studies. There were no relevant effects on the isolated right atrium of guinea pigs *in vitro*, or in the isolated Langendorff-perfused rabbit heart. *In vivo*, positive chronotropic effects were seen in the anesthetized guinea pig after i.v. administration, but not in the conscious dog. In conscious, telemetered dogs, oral bedaquiline had no relevant effects on cardio-hemodynamic and electrocardiogram (ECG) parameters.

Prior to the use of PA-824 in combination with bedaquiline in clinical study NC-001, a preclinical cardiovascular safety pharmacology study was conducted in unrestrained beagle dogs with both drugs to explore the potential for additive effects on QT prolongation induced by the combination. Results indicate that administration of 100 mg/kg bedaquiline daily, for 7 days, causes a small increase in QTc interval by Day 6 in some animals, that is not influenced by the addition of 100 mg/kg PA-824 on Day 7. The effect of PA-824 dosing alone on QT interval appeared to be due to discomfort related to the SC route of administration and not related to the plasma exposure.

2.2.1.2. Bedaquiline Clinical Studies

In the clinical studies conducted to date, a total of approximately 645 Subjects (including 265 healthy volunteers) have been exposed to bedaquiline in the Phase 1 and 2 clinical trials conducted as a part of the development program for the treatment of MDR-TB. An additional 45 subjects received bedaquiline, either as monotherapy (J) or in combination with other agents (J-Pa or J-Z) in study NC-001, and 45 more in study NC-003 (J-Pa-Z, J-Pa-C, J-Pa-Z-C). Four short-term Phase 2a trials enrolled treatment-naïve subjects (C202, TMC207-CL001, NC-001 and NC-003). One long-term, open-label, Phase 2 trial, in MDR-TB Subjects (bedaquiline-TiDP13-C209) and one long-term, Phase 2b trial, consisting of 2 different stages in Subjects infected with newly diagnosed sputum smear-positive pulmonary MDR-TB (bedaquiline-TiDP13-C208), have been completed. The principal findings of these trials are summarized below. Full details of the completed clinical studies are provided in the current bedaquiline IB [12,13] and Sirturo ™ label [11].

The Phase 1 trials have provided a basic understanding of bedaquiline's pharmacokinetic characteristics, drug-drug interaction potential, and short-term safety/tolerability profile in healthy Subjects. Bedaquiline was well absorbed with time to reach the maximum plasma concentration at approximately 5 hours post-dose. The

maximum plasma concentration and AUC increased proportionally up to the highest doses studied (up to 700mg in a single dose-ranging study, 800mg single dose in study bedaquiline-TBC1003 and 400mg q.d. multiple doses). Accumulation from Days 1 to 14 was approximately 2-fold expressed as increase in AUC, while trough concentrations increased up to 3.5-fold. The pharmacokinetics of bedaquiline were comparable between healthy Subjects and Subjects with pulmonary TB. The apparently close to steady-state concentrations in plasma after 14 days of daily treatment is ascribed to the important amount of the drug that is eliminated from the circulation during the ά and β phases of the plasma concentration-time curve. The average terminal elimination half-life of bedaquiline and metabolite M2 noted on extended follow-up after repeat dosing of Subjects with TB infection is about 5.5 months.

Administration of bedaquiline as the tablet formulation with food, increased the relative bioavailability (by 95%) compared to administration without food, and drug-drug interaction trials confirmed the role of cytochrome P450 3A4 (CYP3A4) in the metabolism of bedaquiline to M2. A recently completed study (DMID 10-0043) demonstrated that when given in combination, rifampicin, and to a lesser degree rifabutin, decreased exposure to bedaquiline presumptively due to induction of P450 enzymes. The clinical significance of these findings is unknown, however the current study (NC-005) will not permit the concomitant use of bedaquiline with any rifamycin.

The efficacy of bedaquiline was initially demonstrated in two monotherapy EBA studies C202 and TMC207-CL001. Study C202 was a 7 day study of three daily doses of bedaquiline (25, 100 and 400mg) in treatment-naïve Subjects with MDR-TB. In this study, the 400mg dose group demonstrated positive EBA and was numerically superior to the 25 and 100mg doses. In study TMC207-CL001, doses of 100, 200, 300 and 400mg daily (following a 2-day loading dose) were studied in Subjects with newly-diagnosed pulmonary TB for 14 days. There were no statistically significant differences between the treatment groups, although there was a numerical trend suggesting a positive dose-response relationship. Taken together, these studies establish that bedaquiline monotherapy has EBA in Subjects with TB and that higher doses appear to have greater efficacy.

A 14 day EBA regimen study (TB Alliance Study NC-001-(J-M-Pa-Z)) evaluated bedaquiline administered as monotherapy at 400 mg/d or in combination at that dose with either PA-824 administered at 200 mg/d or weight-adjusted pyrazinamide, to Subjects with pulmonary TB at 2 clinical sites in South Africa. The results indicate that over 14 days, the mean logCFU decreased by 1.3 from baseline in the 15 Subjects given bedaquiline 400 mg/d after a 2 day loading dose. In the cohort of 15 Subjects given bedaquiline 400 mg/d after a loading dose plus weight-adjusted daily doses of pyrazinamide (Z), the mean logCFU decreased by 2.0 logs from baseline, indicating that Z potentiates the early bactericidal effect of bedaquiline. In the cohort with 15 Subjects given bedaquiline 400 mg/d after a loading dose plus 200 mg/d PA-824, the mean logCFU decreased by 1.9. While it appeared that the addition of PA-824 potentiated the anti-tuberculosis activity of bedaquiline, the mean logCFU decrease of the combination was similar to that of PA-824, administered alone at the 200 mg/d dose in the two prior EBA studies of PA-824 monotherapy.

The second 14 day EBA combination study (NC-003), currently undergoing analysis, included a number of bedaquiline-containing arms: bedaquiline, pyrazinamide and clofazimine (J-Z-C), bedaquiline, PA-824 and clofazimine (J-Pa-C), bedaquiline, PA-824, and pyrazinamide (J-Pa-Z) and bedaquiline, PA-824, pyrazinamide and clofazimine (J-Pa-Z-C). Among these, J-Pa-Z had the best activity which was at least as good as the HRZE control. As J-PA-Z is the regimen under study in the current trial (NC-005), this study is discussed in detail in section 2.3.

The long-term efficacy of bedaquiline in Subjects with MDR-TB has been studied in a placebo-controlled, randomized Phase 2b trial (C208) and an open-label, uncontrolled, Phase 2b trial (C209).

In the Phase 2b placebo-controlled trial, C208, the addition of bedaquiline to a 5-drug MDR-TB regimen resulted in significantly faster time to culture conversion compared to placebo. During the 8-week treatment in Stage 1, 47.6% of Subjects in the bedaquiline group became MGIT culture negative compared to 8.7% of Subjects in the placebo group. At Week 24 in Stage 1, after 8 weeks of investigational treatment and 24 weeks

of background treatment, 81.0% of Subjects in the bedaquiline group and 65.2% of Subjects in the placebo group showed treatment success, i.e., completed week 24 and were MGIT negative at this time point.

For C208 Stage 2, in the interim analysis as well as in the primary efficacy analysis, a statistically significant difference in time to culture conversion between the treatment groups ($p < 0.0001$) in favor of bedaquiline was shown. In both analyses, an identical number of Subjects with culture conversion at week 24 (i.e., 24-week responders [missing = failure]) was observed: 78.8% in the bedaquiline group and 57.6% in the placebo group, which was statistically significantly different ($p = 0.008$) based on a logistic regression model with only treatment as covariate. Microbiological response at Week 24 was durable in C208 Stage 2: the percentage of responders (missing = failure) at week 72 was 71.2% in the bedaquiline group and 56.1% in the placebo group.

In the Phase 2b uncontrolled trial, C209, treatment with bedaquiline in combination with an individualized MDR-TB treatment regimen was effective against pulmonary MDR-TB both in newly diagnosed and in non-newly diagnosed Subjects. Culture conversion rates after 24 weeks of treatment with bedaquiline as part of an individualized anti-tuberculosis regimen were higher in Subjects with lower extent of resistance of the *M. Tb* strain and in Subjects with no lung cavitation compared to Subjects with cavitations (in one or both lungs).

2.2.1.3. Bedaquiline Clinical Safety

In the pooled safety data from the 8 Phase 1 trials, bedaquiline was generally safe and well tolerated. In the bedaquiline pooled treatment group, adverse events (AEs) were most frequently related to nervous system disorders and gastrointestinal disorders. The most frequent AE was headache. The most frequent AEs of at least grade 2 were headache, influenza, lipase increased, laceration and hyperuricemia and lipase increased for grade 3, respectively. Three Subjects withdrew due to the following events: a moderate urinary tract infection, pharyngolaryngeal pain and pyrexia, and a grade 3 lipase increase. In a phase I study looking at drug-drug interactions between bedaquiline and either rifampin or rifabutin, 7 Subjects experienced SAEs. Of those Subjects, 5 experienced SAEs of lymphocytopenia (all received Rifabutin), one experienced an SAE of elevated Creatine Kinase (Rifampin arm) and one experienced a grade 4 Total Bilirubin SAE (Rifampin arm). Lymphopenia was previously noted to be an infrequent toxicity associated with rifabutin, but not previously seen with bedaquiline. The bedaquiline/rifabutin regimen demonstrated significant reversible lymphopenia, which did not appear to be related to the AUC or C_{max} of TMC207 or rifabutin.

No deaths occurred in Phase 1 trials. In the Phase 1 trails, one HIV-1 infected Subject experienced 2 serious adverse events (SAEs): (grade 3 diarrhea and dehydration; both SAEs were considered not to be related to bedaquiline, NVP, or N(t)RTIs therapy but to be related to HIV).

In the Phase 2a trial, C202, apart from a suggestion of more QTcF prolongation in the bedaquiline 400mg group, bedaquiline was generally safe and well tolerated. The most commonly reported AE was hemoptysis. Two Subjects in the bedaquiline 400mg group died during the follow-up period. These were a 25-year old female who died due to 2 grade 4 SAEs, i.e., retroviral infection and pulmonary TB, and a 41-year old male, who was prematurely withdrawn from trial due to a positive urinalysis test for cannabinoids and who died due to an episode of massive hemoptysis. There were no other SAEs reported in the bedaquiline group. In the pooled safety data from the placebo-controlled Phase 2b trial, C208, the most frequently reported AEs in the bedaquiline group were nausea, arthralgia, headache, hyperuricemia, and vomiting.

Overall, there was an imbalance in the number of deaths in the pooled Stage 1 and Stage 2 C208 trial. In the pooled analysis (Stage 1 and Stage 2), 12 Subjects in the Any bedaquiline group and 5 Subjects in the Any Placebo group experienced a SAE leading to death; causes of death were varied with only death due to TB reported more than once, and none of these Subjects had a treatment-emergent QTcF ≥ 500 ms. The imbalance in deaths is primarily driven by the C208 Stage 2 results in which the imbalance was 10 bedaquiline Subjects (12.7%) compared to 3 placebo Subjects (3.7%). Based on the pooled results (Stage 1 and 2) while being followed in the placebo-controlled trial, 7 Subjects in the Any bedaquiline group and 1 Subject in the Any Placebo group died. Of these deaths, 1 occurred during the Investigational Treatment phase with bedaquiline/placebo, the remaining deaths occurred afterwards. In the Any bedaquiline group, causes of

death were myocardial infarction, TB (2 cases), alcohol poisoning, hepatitis and hepatic cirrhosis (1 case), septic shock and peritonitis (1 case), and cerebrovascular accident. In the Any Placebo group, cause of death was hemoptysis. The Investigator considered the SAEs leading to death not related to bedaquiline intake in the Any bedaquiline group and doubtfully related to investigational medication in the Any Placebo group. The analysis of long-term follow-up for survival outcomes in Subjects who prematurely discontinued in trial C208 (Stage 1 and 2), based on data collection every 24 weeks (6 months) after withdrawal (up to LSLV in the rollover arm [16 Oct 2012] in Stage 2), included 9 deaths. One Subject in the bedaquiline group (pulmonary TB) and 2 Subjects in the Placebo group (TB-related illness and pulmonary TB) in Stage 1 died, and 4 Subjects in the bedaquiline group (3 Subjects with TB-related illness, 1 Subject motor vehicle accident) and 2 Subjects in the Placebo group (both TB-related illness) died after they discontinued Stage 2 of the trial. None of these Subjects had a treatment-emergent QTcF ≥ 500 ms.

In the uncontrolled Phase 2b trial, C209, the most frequently reported AEs during the investigational phase were hyperuricemia, arthralgia, nausea, vomiting, headache, diarrhea, blood uric acid increased, hypokalemia, pruritus, injection site pain, insomnia, and tinnitus. From start of the trial up to the final analysis, 12 Subjects died during the C209 trial due to SAEs that included TB (5 cases), congestive cardiac failure, renal impairment, lung infection, cardiac arrest (underlying cause pneumonia), hemoptysis, hypertension, and pyopneumothorax/respiratory failure. All of these SAEs leading to death were considered not related to bedaquiline by the Investigator, except for renal impairment that was judged doubtfully related to bedaquiline.

The analysis of long-term follow-up for survival outcomes in Subjects who prematurely discontinued in trial C209, based on data collection every 24 weeks (6 months) after withdrawal, included 4 deaths (all described as TB-related). In total, since the start of the C209 trial 16 Subjects (6.9%) have died (12 Subjects during the trial and 4 Subjects during the survival follow-up phase after premature discontinuation). None of the fatal SAEs were considered related to bedaquiline by the Investigator and none of these Subjects has a treatment-emergent adverse event.

In study NC-001-(J-M-Pa-Z), three Subjects in a bedaquiline-containing treatment arm, were withdrawn. One on a bedaquiline (400mg) only arm for a Grade 3 ALT and GGT elevation although the elevation occurred prior to the first dose of study medication: one on a bedaquiline (400mg) plus pyrazinamide (weight banded) arm for a Grade 3 ALT and AST elevation, and one on a PA-824 (200mg) and bedaquiline (400mg) arm for to a Grade 3 ALT elevation.

Bedaquiline has been recently studied in combination with other agents, including the combination to be studied in the current study (J-Pa-Z), in a 14 day EBA study (NC-003). Because NC-003 forms the basis of moving J-Pa-Z into Phase 2b, findings from this study are presented in section 2.3 Regimens to be Studied.

2.2.2. PA-824

As detailed in the Investigator's Brochure [23], PA-824 is a new chemical entity and a member of a class of compounds known as nitroimidazo-oxazines, which possess significant anti-tuberculosis activity and a unique mechanism of action [24]. PA-824 demonstrated *in vitro* activity against both DS- and MDR-TB [25], and *in vivo* activity in a mouse model of tuberculosis [24,25].

PA-824 has been studied in four 14-day EBA trials to date, including two monotherapy dose-ranging studies and two combination EBA studies. PA-824 monotherapy has demonstrated substantial mycobactericidal activity. The efficacy data from study PA-824-CL-007 indicated that all doses of PA-824 (200, 600, 1000 and 1200mg) produced an equivalent decrease in sputum CFU counts over the 14-day treatment period. In study PA-824-CL-010, an EBA study with a similar design to study PA-824-CL-007 except for the use of lower doses of PA-824 (50, 100, 150 and 200mg/day), results indicated that PA-824 treatment resulted in a measurable dose-dependent mycobactericidal activity over the dose range studied, and supported a clinical dose of 200mg per day. In study NC-001-(J-M-Pa-Z) an EBA study with multiple treatment combinations, the three drug combination of PA-824 (200mg per day), moxifloxacin and pyrazinamide (Pa-M-Z) demonstrated potential as

a treatment shortening regimen and was progressed into an 8 week "SSCC" study (NC-002) in which the combination was shown to be statistically better that the HRZE control on some measures of activity. In the second 14-day combination EBA study (NC-003), the bedaquiline, PA-824 and pyrazinamide (J-Pa-Z) regimen showed promising activity and has been selected to move forward in development and is the focus of the current study (NC-005).

2.2.2.1. PA-824 Preclinical Studies

Microbiology

In vitro studies have demonstrated that the minimum inhibitory concentration (MIC) of PA-824 against a variety of drug-sensitive *M. Tb* 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 *M. Tb*, 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 colony forming unit (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 study (25 mg/kg/day).

Nonclinical Safety Studies

The non-clinical safety evaluation of PA-824 includes pharmacology, pharmacokinetics, toxicology and metabolism studies that were conducted in accordance with current ICH guidelines.

PA-824 was negative in all genotoxicology studies 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 studies were generally mild and reversible; effects were most prominent at 450 mg/kg/day. PA-824 is a weak inhibitor (IC_{50}=20uM) of the hERG channel. In a telemetry monkey study, in the dose range 50-450 mg/kg, there was no or minor prolongation of the QT interval, depending on the method of correction. The weight of evidence suggests that there should be no effect on QT in the dose range being explored in the clinical studies.

Prior to the use of PA-824 in combination with moxifloxacin in the NC-001-(J-M-Pa-Z) study, a preclinical cardiovascular safety pharmacology study was conducted in unrestrained cynomolgus monkeys with both drugs to explore the potential for PA-824 to alter the QT prolongation induced by moxifloxacin. Results indicate that administration of 50 mg/kg PA-824 in combination with 100 mg/kg moxifloxacin resulted in increases in QT and QTc intervals in 1 animal (out of 4 animals tested) that were ~10% higher than administration of 100 mg/kg moxifloxacin alone. Given this limited finding with the relatively high doses of PA-824 and moxifloxacin employed in the preclinical study, and results of ECG monitoring in the EBA study, NC-001-(J-M-Pa-Z), Subjects will not be exposed to undue risk in the proposed clinical study, during which they will also undergo ECG monitoring.

Repeat-dose toxicology studies 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 studies, 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 studies and approximately 200 µg•hr/mL in the 3-month studies.

Reproductive toxicology studies show that PA-824 is not teratogenic in rats or rabbits. In the rat fertility study, 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 study, 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 study in sexually mature males (0, 50, 150, 300 mg/kg/day), and a 6-month rat study (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 studies described above. In each of the later studies, 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 study, although similar drug exposures were attained as in the original 3 month monkey study, 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 study, PA-824 caused irreversible cataracts at 100 mg/kg from Day 118 of the study in males and females. In contrast to the original 3-month rat report, rats in this more carefully conducted study 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 study, the multiple is at least 3.7x.

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

An overall summary of the findings from animal safety and toxicology studies is contained in Table 1.

Table 1: PA-824 Animal Safety and Toxicology Findings

• Nervous system-related effects. Rats given single oral PA-824 doses had decreased body tone, touch responses and decreased grooming behavior at ≥150 mg/kg, which resolved within 24 hours. Rats given repeated daily doses of PA-824 had convulsions, ataxia, hypoactivity, recumbency, hyperactivity and sensitivity to touch, and squinting at ≥100 mg/kg/day, and early deaths occurred at doses ≥500 mg/kg/day. Monkeys given repeated daily doses of PA-824 had hypoactivity, ataxia, tremors, and convulsions at ≥450/300 mg/kg/day. These effects were reversible when dosing stopped and were absent at ≤30 mg/kg/day in rats and ≤150 mg/kg/day in monkeys.
• Testicular toxicity Testicular degeneration/atrophy, occurred in rats with repeated doses of PA-824 at ≥30 mg/kg/day but did not occur in monkeys at any dose level. Testicular effects showed evidence of being partially reversible, albeit very slowly, in rats dosed for 7 days, but not in rats dosed for 14 days. As would be expected, there was a dose-related decrease in fertility in male rats at ≥30 mg/kg/day that was associated with decreased sperm numbers and motility. This effect on fertility in male rats was partially reversible.
• Cataracts Cataracts developed with prolonged daily dosing in rats at PA-824 doses ≥100 mg/kg/day. In one 13-week study in monkeys, cataracts did develop at 450/300 mg/kg/day, but only by the end of a 13-week recovery period. In a second 13-week study in monkeys that included extensive ophthalmic examinations, cataracts did not develop at the high-dose level of 300 mg/kg/day.
• hERG inhibition and QT prolongation PA-824 inhibited hERG current with 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. Co-administration 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.

2.2.2.2. PA-824 Clinical Studies

Phase 1

The safety, tolerability and pharmacokinetics of PA-824 have been studied in 9 Phase 1 studies, which are summarized in Table 2. In these trials, PA-824 has been administered in doses ranging from 50 to 1500mg, as 50 or 200mg tablets or as an oral suspension. PK parameters have largely been consistent in each study 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 – 1000mg, while higher doses achieved minimal additional increases in either C_{max} or AUC.

Two studies using radiolabeled PA-824 in an oral-suspension formulation have been conducted to investigate the metabolism and excretion patterns of PA-824 in humans: Study PA-824-CL-004, which used [benzyl-^{14}C] PA-824 and Study PA-824-CL-008, which used [imidazooxazine-^{14}C] PA-824. The mass balance results from the two studies were very similar. In each study, the majority (53-65%) of radioactivity was excreted in the urine; an additional 26-38% was collected in the feces such that approximately 91% of the administered dose was ultimately recovered in the excreta.

Radioprofiling and metabolite identification work have been completed on samples from the two human studies 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.

Study PA-824-CL-006, a drug-drug interaction study with midazolam to assess the extent of CYP3A inhibition by PA-824, results indicate that dosing of PA-824 400mg 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 Cmax was 0.84 and AUC was 0.85. For the 1-hydroxy midazolam metabolite, the corresponding geometric mean ratio for Cmax 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.

Two additional studies have recently been completed and are currently undergoing analysis: Study DMID 10-0058 (a Thorough QT study comparing PA-824 and PA-824 plus moxifloxacin to moxifloxacin alone) and Study ACTG 5603 (a drug-drug interaction study evaluating the effects of concomitantly administered Efavirenz, Ritonavir-Boosted Lopinavir or rifampicin on the PK parameters of PA-824). The first study found that single doses of PA-824 of 400mg and 1000mg had a small effect on the QTc interval (<5msec) and when PA-824 at 400mg is co-administered with moxifloxacin (400mg) it did not increase the QTc prolongation substantially over what is seen with moxifloxacin alone. The second study found that when administered with Efavirenz, Ritonavir-Boosted Lopinavir, or Rifampin, PA-824 (200mg) median PA-824 concentrations ($AUC_{0\text{-}24h}$) were reduced 35% by EFV, 17% by LPV/r, and 66% by rifampin. The clinical significance of these findings requires further investigation.

Study PA-824-CL-009, a food effects study PA-824 (200mg and 50mg), 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, Cmax and AUC of the 50mg dose increased 1.40-fold and 1.45-fold respectively, whereas for the 200mg dose, Cmax increased 1.76-fold and AUC increased 1.88-fold.

Table 2: PA-824 Phase 1 Clinical Studies

Study	Design	PA-824 Dose	Enrolled	Key Findings
CL-001	Double-blind, placebo-controlled, single-dose, dose-escalating, PK and safety study	0, 50, 250, 500, 750, 1000, 1250, 1500	53	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE.
CL-002	Double-blind, placebo-controlled 7-day multidose, escalating, PK and safety study	0, 200, 600, 1000	24	• Well tolerated; no effects on ECG, vital signs, or PE. • After 5 days' dosing at 1000 mg/d, 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	1000	16	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • Treatment-emergent AEs 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 is 3.5-to-4.5-fold higher when PA-824 is administered within 30 minutes of a high-fat, high-calorie meal than when it is administered after an overnight fast.
CL-004	Open-label, single-dose, ADME	~860, oral suspension [benzyl-^{14}C]PA-824	6	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • No significant radioactivity captured as [benzyl-^{14}C]CO_2. • ~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.

Study	Design	PA-824 Dose	Enrolled	Key Findings
CL-005	Double-blind, 8-day multidose, renal effects	0, 800, 1000	47	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • As anticipated, 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.
CL-006	Open-label, multidose, DDI	400	14	• Well tolerated; no dose-limiting AEs. • For midazolam, the geometric mean ratio of Day 17 (midazolam+Pa-824) vs. Day 1 (midazolam alone) for C_{max} was 0.84 and $AUC_{(0\text{-}infinity)}$ was 0.85. • For the 1-hydroxy midazolam metabolite, the corresponding geometric mean ratio for Cmax was 1.05 and $AUC_{(0\text{-}infinity)}$ was 1.11.
CL-008	Open-label, single-dose, ADME	~1100, oral suspension [imidazooxazine-^{14}C]PA-824	6	• Well tolerated; no dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • No significant radioactivity captured as [imidazooxazine-^{14}C]CO_2. • ~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	50 and 200	32	• Well tolerated; no dose-limiting AEs. • In the presence of high fat, high calorie diet, Cmax and AUC of the 50-mg dose increased 1.40-fold and 1.45-fold respectively, whereas for the 200-mg dose, Cmax increased 1.76-fold and AUC increased 1.88-fold.
A5306	Antiretroviral DDI	200	48	• Based on preliminary data – the study is currently undergoing analysis. • Co-administration with Efavirenz resulted in a 35% reduction in PA-824 AUC. • Co-administration with Ritonavir-Boosted Lopinavir resulted in a 17% reduction in PA-824 AUC. • Co-administration with rifampicin resulted in a 66% reduction in PA-824 AUC.

Study	Design	PA-824 Dose	Enrolled	Key Findings
10-0058	Thorough QT Study	400 and 1000	75	• PA-824, alone and in combination with moxifloxacin, was well tolerated. • 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% CI associated with any LS 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. • No Subject receiving PA-824 or moxifloxacin alone had an observed QTcI value that exceeded 450 ms or experienced a change-from-baseline in QTcI that exceeded 30 ms. • The PK of PA-824 was not affected by the co-administration of moxifloxacin.

- **Phase 2**

Study PA-824-CL-007, a 14 day monotherapy EBA study, indicated that all doses of PA-824 (200, 600, 1000 and 1200mg a day) produced a measurable and equivalent decrease in sputum CFU counts over the 14-day treatment period. Study PA-824-CL-010 was an EBA study with a similar design to study PA-824-CL-007 except for the use of lower doses of PA-824 (50, 100, 150 or 200 mg/day). Results indicate that PA-824 treatment resulted in a measurable dose-dependent mycobactericidal activity, with the 50mg dose demonstrating less activity than the 100, 150 and 200mg doses, which were all equivalent.

Study NC-001-(J-M-Pa-Z) was a 14 day EBA study that assessed the two-week EBA of the following drug combinations: PA-824 plus pyrazinamide, PA-824 plus pyrazinamide plus moxifloxacin, along with two other non-PA-824 containing combinations. Results indicate that the three drug combination of PA-824 (200mg per day), moxifloxacin and pyrazinamide has potential as a treatment shortening regimen. In the study this three drug combination has an EBA 0-14, which is believed indicative of sterilizing activity, numerically better than the current 4-drug intensive phase treatment of HRZE.

The recently completed Phase 2b study, NC-002, was a multi-center open-label partially randomized clinical trial with four treatment groups. Subjects with drug-sensitive TB were randomized to receive moxifloxacin 400mg plus PA-824 100mg plus pyrazinamide 1500mg (M-PA100-Z) or moxifloxacin 400mg plus PA-824 200mg plus pyrazinamide 1500mg (M-PA200-Z) or standard HRZE therapy. HRZE was included as a control arm for the drug-sensitive treatments and for the laboratory methodology. Subjects with MDR-TB received moxifloxacin 400mg plus PA-824 200mg plus pyrazinamide 1500mg (M-PA200-Z MDR). The study population included a total of up to 230 male and female newly diagnosed Subjects with drug-sensitive or multi drug-resistant, smear positive pulmonary tuberculosis aged 18 to 65 years (inclusive). The primary efficacy endpoint was the rate of change in the logarithm of colony forming unit (CFU) (or log[CFU]) count) over 8 weeks of treatment analysed by a Joint Bayesian Non-linear Mixed Effect (NLME) regression.

Preliminary analyses indicate that a total of 207 Subjects were enrolled, with 60 randomized to M-PA100-Z, 62 randomized to M-PA200-Z, and 59 to HRZE. An additional 26 Subjects were treated in the M-PA200-Z MDR-TB arm. Of note, more Subjects in the MDR-TB arm did not complete the full 8 weeks of treatment, primarily because many were withdrawn as late-exclusions (*M. Tb* resistant to pyrazinamide determined in culture after enrolment in the study). 21 MDR-TB Subjects were in the study with active treatment through day 14 and 10 were in the study through the full 8 weeks of treatment (9 with evaluable results for the primary microbiological endpoint). In contrast, the following number of Subjects was in the study with active

treatment through 8 weeks in the 3 randomized arms with evaluable results for the primary microbiological endpoint: 55 in the M-PA100-Z arm, 54 in the M-PA200-Z arm and 54 in the HRZE arm. For the primary endpoint, Subjects in the M-PA200-Z arm had a statistically significantly greater decline in the log CFU count over the 8 weeks, than the Subjects in the HRZE arm.

Finally, PA-824 has recently been studied in combination with Bedaquiline and other agents in a 2 week EBA study (NC-003). Findings from this study form the basis for selecting the J-Pa-Z regimen for further study in the current clinical trial (NC-005) and are discussed in detail in section 2.3 Regimens to be Studied.

Table 3: PA-824 Phase 2 Studies

Study	Design	PA-824 Doses	Enrolled	Key Findings
CL-007	Partially double-blinded (blinded as to PA-824 dose), 14-day multidose, extended early bactericidal activity.	200, 600, 1000, 1200	69	• Overall well tolerated with relatively few AEs and no dose-limiting AEs or laboratory findings. No clinically significant effects on ECG, vitals, or PE noted. • Two SAEs occurred during study, both were considered possibly related to TB disease (hemoptysis). • PA-824 treatment produced a measurable decrease in log CFU, with the magnitude of effect equivalent for all doses.
CL-010	Partially double-blinded (blinded as to PA-824 dose), 14-day multidose, extended early bactericidal activity.	50, 100, 150, 200	69	• Well tolerated. • PA-824 treatment produced a measurable decrease in log CFU with some evidence of dose dependence.
NC-001	Partially double-blinded (blinded as to combination within Pa or J containing arms), 14-day multidose, extended early bactericidal activity.	200	85	• Well tolerated. • PA-824 plus moxifloxacin plus pyrazinamide combination treatment produced a decrease in log CFU at least comparable to that of the Rifafour e-275® control group.
NC-003	Multi-center, open-label, randomized clinical trial with seven parallel treatment arms. Fifteen Subjects were enrolled in each of the following treatment arms: TMC207 plus PA-824 plus pyrazinamide plus clofazimine, TMC207 plus PA-824 plus pyrazinamide, TMC207 plus PA-824 plus clofazimine, TMC207 plus pyrazinamide plus clofazimine, pyrazinamide alone, clofazimine alone, and Rifafour e-275®.	200	105	• Based on preliminary results: • The EBA results for Rifafour® in this trial are similar to those reported in prior studies and validate the trial's underlying mycobacterial methodology; the decrease in log(CFU) count over the 14-day treatment period under Rifafour® was similar to the decreases observed in previous studies. • Among the regimens studied, the combination J-PA-Z demonstrated the highest EBA, with results at least comparable to the HRZE control. • The treatments administered in this trial were well tolerated by the trial population. • No deaths were reported in this trial. Serious AEs were reported for 1 Subject (1.0%) in the clofazimine alone arm: gastroenteritis, anemia, and deep vein thrombosis (none of which were considered to be related to the treatment).

Study	Design	PA-824 Doses	Enrolled	Key Findings
NC-002	Multi-center open-label partially randomized clinical trial in four treatment groups. Subjects with drug-sensitive TB randomized to receive moxifloxacin 400 mg plus PA-824 100 mg plus pyrazinamide 1500 mg or moxifloxacin 400 mg plus PA-824 200 mg plus pyrazinamide 1500 mg or Rifafour e-275®.	100, 200	207	• Based on preliminary results: • For the primary endpoint Subjects in the M-PA200-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 *M. Tb* on solid culture than on liquid culture. Subjects in both of the M-Pa-Z 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 M-PA100-Z group, 92% in the M-Pa-Z group, 85% in the Rifafour® group and 89% in the M-Pa-Z MDR group • Eleven serious adverse events (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 study drug regimen and the death was not considered related to study drug by the Investigator or the sponsor. Four other SAEs were considered not related to study drug, including a pneumothorax, a bone fracture, dyspnea requiring hospitalization, and second degree heart block SAEs considered possibly related or related to the study drug regimen included hyperuricemia likely secondary from pyrazinamide, drug-induced hepatitis and elevated liver enzymes. One Subject had an episode of agranulocytosis that resolved after the study drug regimen was stopped and one Subject had a seizure and was discontinued from the study.

2.2.2.3. Clinical Safety

The overall safety profile determined from the clinical studies completed to date indicates PA-824 is well tolerated in healthy adults and in TB Subjects when administered alone and in combination with moxifloxacin, pyrazinamide, bedaquiline and clofazimine. Single doses ranging from 50 to 1500 mg in men and daily doses in men and women up to 1200 mg for up to 14 days were safe and resulted in generally minor adverse events (AEs). Approximately 80% of AEs were mild, with most of the remainder as moderate. Among healthy volunteers dosed to date, one severe AE and no serious adverse events (SAEs) have been observed.

In Phase 1 trials at the clinical dose of 200mg or lower, the incidence of headache was approximately 20-30% and similar to placebo. At doses of 800mg and higher, usually in trials without a placebo or comparator arm, the incidence of headache reached 80%. Headache occurrence was typically higher in studies with longer confinement periods. Throughout the development program, other common TEAEs include elevated serum creatinine, stomach discomfort (including nausea and other gastrointestinal symptoms such as flatulence and/or diarrhea), and skin and subcutaneous tissue disorders (including erythema, pruritus and rash). Skin and subcutaneous tissue disorders, followed by stomach discomfort were the most commonly reported TEAEs in the Phase 2 monotherapy studies (PA-824-CL-007 and PA-824-CL-010). Within Study PA-824-CL-007, a higher incidence of PA-824 TEAEs were observed in the higher PA-824 dose groups (PA-824 200mg: 7%; PA-824 600mg: 13%; PA-824 1000mg: 31%; and PA-824 1200mg: 33%). The incidence of the TEAEs in the Rifafour® treated group was 25%. Study PA-824-CL-010, among the four PA-824 treatment groups (50mg, 100mg, 150mg, and 200mg) and the Rifafour® treatment group, a higher incidence of TEAEs was observed in the 50mg PA-824 group (66.7%) when compared with Rifafour® (50.0%) and the other PA-824 treatment groups. For the multidose, placebo-controlled Studies PA-824-CL-002 and PA-824-CL-005, overall AE frequency tended to be greater among PA-824 Subjects than among placebo Subjects, and tended to be higher in higher PA-824 dose groups.

Study PA-824-CL-005 was undertaken to determine the mechanism responsible for the elevation in serum creatinine seen with PA-824 dosing in studies PA-824-CL-001 and PA-824-CL-002. This study explored the effects of PA-824 on kidney function by measuring glomerular filtration rate (GFR), effective renal plasma flow (ERPF), filtration fraction (FF, calculated as GFR/ERPF), and creatinine clearance. Subjects were dosed in blinded fashion with placebo, 800mg PA-824, or 1000mg PA-824 for 8 days. Serum creatinine levels rose in both the 800- and 1000-mg/day PA-824 groups, by an average of 0.18 mg/dL (19%) and 0.25 mg/dL (27%) in the two groups respectively by Day 8; the largest individual increase was approximately 40% over baseline. In this study, although serum creatinine levels rose, no meaningful effects were noted during the dosing period on GFR, ERPF, BUN, uric acid or FF. As expected, creatinine clearance was reduced concomitantly with maximally elevated serum creatinine levels relative to baseline. Taken together, these results indicate that PA-824 does not negatively affect renal function. Instead, the drug can be assumed to cause its effects on serum creatinine by inhibiting tubular creatinine secretion; such an effect has been reported with other approved drugs (e.g. cimetidine) and is not considered clinically significant.

Across all studies, the great majority (>~95%) of AEs resolved without sequelae. In Study PA-824-CL-003, one Subject concluded the study with blurry/double vision that may have been related to childhood strabismus, while another Subject had ongoing swollen fingers on both hands at the end of the study. In Study PA-824-CL-007, two Subjects exited the study with an ongoing AE (anemia [mild, unrelated] and rash [mild, related]) and the outcomes for three AEs in one Subject each (anemia [mild, possibly related], elevated LFT [moderate, unrelated], and Wolff-Parkinson-White syndrome [mild, unrelated] were not known due to loss to follow-up. In Study PA-824-CL-005, one Subject treated with 800mg PA-824 was discharged with three ongoing AEs (proteinuria [nephrotic range during the study, but non-nephrotic range in follow-up], hypoalbuminemia, and iron deficiency). The proteinuria and hypoalbuminemia were moderate in severity and the iron deficiency was mild. This Subject substantially improved, and the Subject is seen periodically by a nephrologist. A renal biopsy performed 20 months post-study revealed focal segmental glomerulosclerosis likely secondary type, although the Subject remains fundamentally healthy with normal renal function indices and no signs of peripheral edema or hypertension. A complete review of her screening and check-in laboratory values suggests, in the

opinion of the Sponsor, that she might have had a pre-existing undiagnosed clinical condition including atypical lipid profile, BUN below the lower limit of the normal range, and ALT and AST above the upper limit of normal range. Furthermore, her eosinophil count was above-normal at Screening at 6.7% and progressively rose during the study to 8.9% by Day 15 and she reported a personal and family history of allergies and rhinorrea. The Investigator considered this individual normal and meeting the protocol entry criteria, and enrolled this Subject. In study PA-824-CL-010 there were 5 mild events (papular rash, left bundle branch block, pruritis, pruritis general, peripheral neuropathy) in 5 Subjects being administered PA-824 which were not resolved at study completion. In addition, there were 3 moderate events (heart rate increased, hyponatremia and hemoglobin decreased) in 3 Subjects being administered PA-824 which were not resolved, lost to follow up or improved, respectively. There was a single event in one Subject being treated with Rifafour® (lens opacity) which was not resolved at study completion.

Among the healthy volunteers tested, any concomitant therapy for AEs was generally palliative in nature. Occasionally, pains such as headaches, sore throat, and muscle ache were treated with analgesics. One instance of iron deficiency (deemed not related to study drug) was treated with an iron supplement. In studies PA-824-CL-007 and PA-824-CL-010, multiple AEs, most of which were associated with ongoing TB disease, were treated with medications or other interventions including hospitalization (e.g., to treat hemoptysis, pneumonia and pneumothorax).

In most of the completed Phase 2 studies, no Subjects discontinued from the study as a result of AEs. In Study PA-824-CL-002, dosing for all Subjects in the 1000mg dose group was discontinued on Day 5 in response to rising serum creatinine levels. In Study PA-824-CL-005, one Subject was discontinued for safety reasons in relation to a severe rash that developed approximately 32 hours after the 8th and last dose of PA-824 (1000mg). The rash symptoms were treated with diphenhydramine, prednisone, and hydroxyzine at various points during the ensuing approximately 9 days until the symptoms completely resolved. In Study PA-824-CL-007, two Subjects (one in the 200 mg/day PA-824 group and one in the control arm) were discontinued as a result of disease-related hemoptysis. Each of these events was classified as an SAE, both resolved with treatment in hospital and neither was considered possibly related to the study drugs. In Study PA-824-CL-010, one Subject was withdrawn due to the SAE of pneumothorax after 4 days' dosing, which resulted in hospitalization and later resolved. The SAE was deemed related to the Subject's concurrent tuberculosis and unrelated to PA-824.

Post-study follow-up ophthalmic examinations were performed on Subjects and Subjects enrolled in two studies (PA-824-CL-005 [n=30] and PA-824-CL-007 [n=46]) where Subjects received the highest doses of PA-824 for the longest duration among the clinical studies conducted to date. Male and female healthy volunteers were treated at doses up to 1000 mg/day for 8 days in study PA-824-CL-005, and male and female TB Subjects were treated at doses up to 1200 mg/day for 14 days in study PA-824-CL-007. Two ocular events were reported, one cataract was among the 12 Subjects from the 1200 mg PA-824 group in study PA-824-CL-007 and the other cataract was from among the 5 Subjects within the HRZE group.

In NC-001-(J-M-Pa-Z), five Subjects were discontinued prior to completion of their treatment with a PA-824 containing arm. One Subject receiving PA-824 (200mg), moxifloxacin (400mg), and pyrazinamide (dosed by weight) experienced an SAE considered by the Investigator unrelated to the drug combination. The SAE consisted of convulsion as well as aggressive and violent behaviors. After a CT scan, the Subject was diagnosed with neurocysticercosis. A second Subject receiving PA-824 (200mg), moxifloxacin (400mg), and pyrazinamide (dosed by weight) was withdrawn on Treatment Day 5 based on a protocol specified criterion of an increase from baseline in QTcF and QTcB greater than 60 msec on repeated ECGs and accompanied by clinically relevant T-wave morphology changes. On Day 5, the Subject had prolonged QTc values (>60 msec) on the pre-dose ECG; however, on repeat ECGs, the QTc values stabilized satisfactorily. Five hours post-dose on Day 5, ECG QTc values were again increased (>60 msec) from baseline and repeat ECGs also revealed T-wave changes. The Subject was, therefore, withdrawn from the study as specified in the protocol. In addition, two Subjects receiving PA-824 (200mg), and pyrazinamide (dosed by weight) were withdrawn due to Grade 3 ALT levels, although the elevation in ALT in one of these Subjects occurred prior to the first dose of study medication.

One Subject receiving PA-824 (200mg) and bedaquiline (400mg) was withdrawn due to a Grade 3 ALT elevation. Overall in the trial, 53% of the 15 Subjects in the PA-824 + pyrazinamide treatment arm experienced treatment-emergent adverse events, as compared with 53% of the 15 Subjects in the PA-824 + pyrazinamide + moxifloxacin arm and 25% of the 8 Subjects in the HRZE (control) arm. All of these adverse events were rated by the Investigator as mild or moderate. 7% of Subjects in the PA-824 + pyrazinamide treatment arm experienced liver enzyme elevations, as compared with 20% of Subjects in the PA-824 + pyrazinamide + moxifloxacin arm and 0% in the Rifafour® arm, accounting for most of the imbalance between groups. All liver enzyme elevations were < 3x ULN except for two cases.

Also in NC-001-(J-M-Pa-Z), changes in QT interval were assessed pre-dose and at 2hrs and 5 hrs post-dose on each day of the study for the PA-824 + pyrazinamide and PA-824 + pyrazinamide + moxifloxacin treatment arms. On Day 14, the last dosing day, no Subject in either treatment group had a corrected QT interval (QTcF) > 450 msec. One Subject in the PA-824 + pyrazinamide arm had a QTcF increase of between 30 and 60 msec; no Subject had a QTcF increase > 60 msec. No Subjects in the PA-824 + pyrazinamide + moxifloxacin had a QTcF increase > 30 msec.

Preliminary data analyses of the study NC-002 indicate that a total of 207 Subjects were enrolled, with 60 randomized to M-PA100-Z, 62 randomized to M-PA200-Z, and 59 to HRZE. An additional 26 Subjects were treated in the M-PA200-Z MDR-TB arm. In this study 88% of all Subjects had a treatment emergent adverse event (TEAE), including 87% in the M-PA100-Z group, 92% in the M-PA-Z group, 85% in the HRZE group and 89% in the M-PA-Z MDR-TB group. Adverse events were graded according to the NIH Division of Microbiology and Infectious Diseases Adult Toxicity Table.

Eleven serious adverse events (SAEs) were reported in 9 Subjects, with one Subject in each of the M-PA100-Z and the HRZE 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 study drug regimen and the death was not considered related to study drug by the Investigator or the Sponsor. Four other SAEs were considered not related to study 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 study drug regimen included hyperuricemia likely secondary from pyrazinamide, drug-induced hepatitis and elevated liver enzymes. One Subject had an episode of agranulocytosis that resolved after the study drug regimen was stopped and one Subject had a seizure witnessed by the family and was discontinued from the study.

The protocol required that Subjects with hepatic enzyme ALT or AST elevations greater than 3X the Upper limit of Normal (ULN) must have study drug discontinued. Consequently, 25 Subjects were withdrawn from the study across the study arms for elevations in hepatic enzymes. The distribution of elevations in ALT across the study arms is presented in Table 4. While more Subjects in the M-PA200-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 drug-sensitive *M. Tb*.

Table 4: NC-002 Elevations in Alanine Aminotransferase

ALT	Statistic	M-PA100-Z (N=60)	M-PA200-Z (N=62)	HRZE Control (N=59)	M-PA200-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

Ophthalmologic Evaluations – All Subjects received ophthalmologic evaluations using the AREDS2 grading system across a range of 0-4 including visual acuity testing and slit lamp examinations at baseline and 3 months after completion of study drug dosing. 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 M-PA100-Z group and 3 Subjects in the M-PA200-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 – In study NC-002 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 study drug regimen caused testicular toxicity, the most sensitive measure from these hormones would be an increase in levels of FSH. Among Subjects in the M-PA100-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 M-PA200-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® 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 M-Pa-Z regimen is not likely to cause testicular toxicity in men.

Electrocardiographic Conduction Interval Changes – Subjects in NC-002 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 study. A small number of Subjects had asymptomatic increases in QTcF from baseline over 60 msec: Two in the M-PA100-Z group, 4 in the M-PA200-Z group, none in the Rifafour® group and 2 in the M-PA200-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® group, 11.1 in the M-PA100-Z group, 17.8 msec in the M-PA200-Z group and 6.7 in the M-PA200-Z MDR-TB group. Of note, many Subjects were tachycardic at baseline with their active pulmonary *M. 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.

PA-824 has been studied in combination with bedaquiline in study NC-003; the results of this study are presented in detail in section 2.3 Regimens to be Studied.

2.2.3. Moxifloxacin

Moxifloxacin (M) is an 8-methoxyquinolone whose oral formulation (which will be used in this study) 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, and skin and soft tissue infections. It 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 400mg. Clinical studies have been carried out in additional indications (urinary tract infections, pelvic infections, pharyngitis/tonsillitis, and tuberculosis).

Studies in murine models of TB and in TB Subjects have shown that moxifloxacin has significant mycobactericidal activity [26-35]. These include EBA studies as well as four 8-week treatment period Phase 2b studies in which moxifloxacin was substituted for either isoniazid or ethambutol in the standard, first-line, TB treatment regimen (see Table 5). Currently, a Phase 3 trial, REMoxTB, is ongoing in which moxifloxacin replaces either isoniazid or ethambutol in first-line treatment and is administered in combination with the other first-line drugs for four months, with the expectation that total treatment duration of drug-sensitive TB can be shortened to four months. The dose of moxifloxacin employed in these TB clinical trials and the NC-001, NC-002and NC-003 studies is 400mg daily, the registered dose (for other indications as stated above) and

the dose that is commonly used as second line therapy for TB (e.g., in MDR-TB Subjects). This is the same dose we plan to use in the proposed study.

2.2.3.1. Moxifloxacin Clinical Studies

Moxifloxacin is commonly used as second line therapy for TB in Subjects (e.g. MDR- TB), and has also been evaluated in several clinical studies of Subjects with TB, including four 8-week treatment period Phase 2b studies (see Table 5 below).

Table 5: Summary of Phase 2b studies in which moxifloxacin were administered as part of a four-drug regimen during the intensive phase of treatment (total treatment duration: 2 months)

Study	Design	Objective	Subjects (N)	Status
Study 27	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	Completed
OFLOTUB Study	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	Completed
Johns Hopkins (FDA orphan drug) Study	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	Completed
Study 28	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	Completed

2.2.3.2. Moxifloxacin Clinical Safety

In Study 27 [32], 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 study treatment. Subjects treated with the 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 study 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 study [33], 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%), hypokalemia (6%) and vomiting (5%). No Subject was withdrawn from the study due to an adverse event. There were 4 deaths in the study: 2 in the control group, 1 each in the moxifloxacin and ofloxacin arms. Importantly, Subjects in this study 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 study [34], 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 study drug (grade 3 cutaneous reaction in the ethambutol group). Eight Subjects died during the study, including 1 in each group still receiving study phase treatment. No death was attributed to study 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 E 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 Study 28 [35], the proportions of Subjects with SAEs during the intensive phase treatment were similar between arms (isoniazid 3.9% vs. moxifloxacin 4.2%; P = 0.88). Three SAEs attributed to study treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group. Seven Subjects died during the study including 3 Subjects receiving the moxifloxacin treatment regimen and 4 Subjects receiving the isoniazid treatment regimen. All 3 moxifloxacin Subjects died during the intensive phase of TB treatment. Two Subjects died from advanced pulmonary TB judged not related to study treatment and 1 Subject (who developed diabetic ketoacidosis considered possibly related to study treatment) died from possible acute pulmonary embolus unrelated to study treatment. The 4 isoniazid deaths occurred during the continuation phase, and all 4 were considered unrelated to study 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 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). Moxifloxacin has also been evaluated in combination with PA-824 for two weeks in Subjects with TB (Trial NC001) and for 8 weeks in NC002 as reviewed above in Section 2.2.3 (Trial NC-001).

For additional information on moxifloxacin, refer to the IB [36] and the manufacturer's package insert [37].

2.2.4. Pyrazinamide

Pyrazinamide, the pyrazine analogue of nicotinamide, is an approved anti-tuberculosis agent. Pyrazinamide is indicated for the initial treatment of active tuberculosis in adults and children when combined with other anti-tuberculosis agents and it contributes significantly to the sterilization of lesions and thus, treatment shortening [38].

The current study is being conducted as part of the clinical development of PA-824 and bedaquiline-based combinations to treat TB. In mouse model studies of TB, the combination of PA-824 and pyrazinamide displayed anti-tuberculosis activity that was equivalent to that of the first-line regimen of rifampicin, isoniazid and pyrazinamide [39]. Murine studies have also demonstrated that pyrazinamide potentiates the bactericidal effect of bedaquiline and is a key contributor to the efficacy of many combination regimens. Thus, the novel pyrazinamide containing regimens in this study, which contain neither isoniazid nor rifampicin, may have the potential to (1) shorten the duration of TB chemotherapy and (2) treat both drug-sensitive and multi drug-resistant TB.

Pyrazinamide has been used in standard regimens to treat TB for a number of years and is commonly administered to Subjects with drug-sensitive TB for the intensive first 2 months of a regimen in combination with isoniazid, ethambutol and rifampicin. Pyrazinamide has been evaluated in two EBA studies of two and 14 days, respectively [2, 41]. Both studies showed that there is little activity against tuberculosis in the first two days. However, in a study of 9 Subjects taking 2 grams daily of pyrazinamide, the daily average logCFU count decreased to a similar amount as Subjects in other trial arms who were taking rifampicin, streptomycin or INH as monotherapy [41].

Pyrazinamide monotherapy has been evaluated in a 14 day EBA study in Subjects with DS-TB (study NC-003-(C-J-Pa-Z). In this study, the pyrazinamide monotherapy arm demonstrated modest EBA over the 14 days of the study, consistent with earlier studies. NC-003 also included the combinations of pyrazinamide and bedaquiline and those results will be summarized below in section 2.3 Regimens to be Studied.

Risks associated with the use of pyrazinamide are highlighted in section 2.5.3.

2.3. Regimens to be Studied

The regimens included in this study (J-Pa-Z and J-Pa-M-Z) have been selected based on the performance of J-Pa-Z in clinical study NC-003 and mouse models of pulmonary TB. The regimen J-M-Pa-Z will be administered only to MDR-TB Subjects enrolled into the study; moxifloxacin has been added to the J-Pa-Z regimen for these Subjects because of the high rate of pyrazinamide resistance seen in MDR-TB Subjects in the NC-002 study. It essentially provides protection against the development of new resistance to the J-Pa-Z study drugs. These regimens have the potential to shorten TB treatment to less than 4 months for Subjects sensitive to the individual drugs in the regimens, including some MDR-TB Subjects. These are oral regimens, removing the need for injectables as part of MDR-TB treatment and also project to be markedly less expensive than current MDR-TB therapy. Additionally, these regimens can be administered in a fixed dose for all patients, and will therefore be simpler for health systems to deliver and patients to use.

The key data supporting the progression of J-Pa-Z into Phase 2b (NC-005) are the results of clinical study NC-003, which is described below.

2.3.1. Non-clinical Studies

In the murine model of TB, addition of J to HRZ results in accelerated clearance of *M.Tb* [12,13] when compared to HRZ alone. There appears to be a synergistic interaction with Z: 100% of mice were culture negative after 8 weeks of treatment with J and Z compared to 0% of mice treated with the standard regimen of HRZ [18]. Collectively, these findings in the mouse model have led to the suggestion that regimens containing J and Z could be effective in the treatment of both DS and MDR-TB and shorten treatment duration in patients.

While the combination of J and Pa in the murine model of TB appeared somewhat antagonistic relative to J alone, it was as active as the triple combination of HRZ [18] and in a subsequent study it was more active in the mouse model than HRZ [19]. Thus a novel regimen with a J plus Pa core could be effective in the treatment of MDR-TB by providing two novel drugs for which there is no known pre-existing resistance. Indeed, while JPaZ was less effective than the JZ regimen in CFU reduction in the first month of therapy due to the antagonism between J and Pa, the JPaZ regimen resulted in a treatment duration of 3 months in the murine model compared to the 6 months required for the standard of care, HRZ.

Prior to the use of PA-824 in combination with J in clinical study NC-001, a preclinical cardiovascular safety pharmacology study was conducted in unrestrained beagle dogs with both drugs to explore the potential for additive effects on QT prolongation induced by the combination. Results indicate that administration of 100 mg/kg J daily for 7 days causes a small increase in QTc interval by Day 6 in some animals that is not influenced by the addition of 100 mg/kg Pa on Day 7. The effect of PA-824 dosing alone on QT interval appeared to be due to discomfort related to the subcutaneous route of administration and not related to the plasma exposure.

2.3.2. Clinical Study NC-003 – Preliminary Results

Efficacy

In the 14 day EBA study NC-003-(C-J-Pa-Z) two monotherapy and four different combinations of J, Pa, Z and C were evaluated in DS-TB Subjects. Fifteen Subjects were randomized into 7 treatment arms: C, Z, J-Pa-Z-C, J-Pa-Z, J-Pa-C, J-Z-C, and HRZE control. This study demonstrated no EBA for the clofazimine monotherapy arm and modest EBA for the pyrazinamide monotherapy arm. However, all of the experimental regimens demonstrated EBA. In general, adding clofazimine to the various agents resulted in either no increase in EBA, or a decrease when compared to a similar regimen that did not include clofazimine. In this study, the

experimental regimen with the best EBA was J-Pa-Z which demonstrated a rate of decrease in both logCFU and logTTP that was at least as good as the HRZE control. The daily logCFU results are presented in Table 6. Similar results were found when TTP was used to calculate the BA(0-14).

Table 6: NC-003 Efficacy Results: Daily BAlogCFU(0-14)

Arm	logCFU
JPaZC	.124
JPaZ	.180
JPaC	.086
JZC	.098
Z	.036
C	-.025
Rifafour®	.152

Safety

In the 14 day EBA study NC-003-(C-J-Pa-Z) two monotherapy and four different combinations of J, Pa, Z and C were evaluated in DS-TB Subjects. Generally, the regimens in this study were well tolerated. Table 7 provides a list of the overall safety findings. The only SAE experienced in the study was in a Subject in the clofazimine monotherapy arm. Otherwise, the rates of treatment emergent AEs (TEAEs) were similar across the treatment arms. One Subject withdrew from the study due the an adverse event: in the J-Pa-Z arm a Subject had increased liver function tests (ALT, AST and GGT) and was withdrawn from the study.

Table 7: NC-003 Safety Data

	JPaZC	JPaZ	JPaC	JZC	Z	C	HRZE	Total
N	15	15	15	15	15	15	15	105
Subjects with:								
TEAEs	11	9	8	10	10	9	8	65
TEAEs leading to death:								
Serious TEAEs						1		1
TEAES leading to early withdrawal		1						1
TEAEs leading to discontinuation of study drug		1						1
Drug-related TEAES	8	5	7	3	5	6	5	39
Serious, drug-related TEAEs								
Grade III AEs		2	1	2		1		6
Grade IV AEs		1	1					2
Grade II/IV AEs		2	1	2		1		6

QT Prolongation

Because bedaquiline and clofazimine are both known to prolong the QT interval, intensive ECG monitoring was included in the study endpoints. The mean change from baseline in QTcB and QTcF tended to be larger at 5 hours than at 10 hours post-dose in the (J-Pa-Z-C) arm and in the (J-Pa-C) arm. No QTcB or QTcF ≥500 ms were reported. An increase from baseline to Visit 5 and subsequent visits of ≥60 ms in QTcB was reported for 2 Subjects in the (J-Pa-C) arm and for 1 Subject in the clofazimine alone arm. An increase from baseline to Visit 5 and subsequent visits of ≥60 ms in QTcF was reported for 4 Subjects in the (J-Pa-C) arm and for 1 Subject in the clofazimine alone arm. For both QTcB and QTcF, the (J-Pa-Z-C) arm and the (J-Pa-C) arm showed the largest increase from baseline. In the current study (NC-005), clofazimine will not be used in any treatment arms.

2.4. Control: HRZE

The HRZE combination is indicated and commonly used for the treatment of drug-sensitive TB. One cohort of Subjects in this study will be given standard weight-adjusted doses of HRZE tablets as a control for the BA quantitative mycobacteriology and to evaluate whether HRZE in this population gives similar BA results to that demonstrated in prior studies with this combination. Please see the HRZE package insert for more information [40].

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

2.5.1. Bedaquiline

In the clinical studies conducted to date, a total of approximately 645 Subjects (including 265 healthy volunteers) have been exposed to bedaquiline in the Phase 1 and 2 clinical trials conducted as a part of the development program for the treatment of MDR-TB. An additional 60 subjects received bedaquiline in a monotherapy EBA study of 14 days (study TMC207-CL001) 45 Subjects received bedaquiline, either as monotherapy (J) or in combination with other agents (J-Pa or J-Z) in study NC-001 and 45 more in study NC-003 (J-Pa-Z, J-Pa-C, J-Pa-Z-C). In these studies, bedaquiline has been shown to be an effective treatment for Subjects with both DS and MDR-TB. Specifically, the regimen J-Pa-Z was demonstrated to have efficacy at least as good as the HRZE control in study NC-003. Furthermore, bedaquiline is a novel agent with no pre-existing resistance and, based on mouse model data, may result in shortened treatment durations when included in novel regimens to treat both DS- and MDR-TB. Based on the combined experience in these clinical studies, the following known and potential risks have been identified.

Adverse Drug Reactions for bedaquiline

During the Investigational Treatment phase in the controlled trials, the most frequently reported ADRs in the Any bedaquiline group (> 10.0% of Subjects) were nausea (36 [35.3%] Subjects), arthralgia (30 [29.4%] Subjects), headache (24 [23.5%] Subjects), vomiting (21 [20.6%] Subjects), and dizziness (13 [12.7%] Subjects). In the placebo group, nausea was reported in 27 (25.7%) Subjects, arthralgia in 21 (20.0%) Subjects, headache in 12 (11.4%) Subjects, vomiting in 24 (22.9%) Subjects, and dizziness in 12 (11.4%) Subjects. A greater percentage of Subjects in the Any bedaquiline group compared to the Any Placebo group (difference > 5.0%) had headache (23.5% versus 11.4%, respectively), nausea (35.3% versus 25.7%, respectively), arthralgia (29.4% versus 20.0%, respectively), and transaminases increased (6.9% versus 1.0%, respectively). A greater percentage of Subjects in the Any Placebo group compared to the Any bedaquiline group (difference > 5.0%) had diarrhea (11.4% versus 5.9%, respectively).

Mortality

In the 120-week C208 Stage 2 trial where bedaquiline was administered for 24 weeks in combination with a background regimen, more deaths occurred in the bedaquiline group than in the Placebo group. After enrolment, 10 Subjects died in the bedaquiline treatment group (N = 79) compared to 3 Subjects in the placebo group (N = 81). One death occurred during administration of bedaquiline. The median time to death for the remaining 9 Subjects was 344 days after last intake of bedaquiline. One of the 10 deaths in the bedaquiline

group occurred after the week 120 window. In the bedaquiline group, the most common cause of death as reported by the Investigator was TB (5 Subjects). For all 5 deaths due to TB, the Subject's last microbiological outcome was either failure to convert or relapse. The causes of death in the remaining bedaquiline Subjects varied. The imbalance in deaths is unexplained. In addition, no discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat TB, human immunodeficiency virus (HIV) status, or severity of disease was observed.

Cardiovascular safety

During clinical trials with bedaquiline a prolongation of QTc interval was observed. An ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.

Bedaquiline treatment initiation is not recommended in patients with:

- Heart failure;
- QTcF interval > 450 ms (confirmed by repeat electrocardiogram);
- A personal or family history of congenital QT prolongation;
- Concomitant administration of fluoroquinolone antibiotics that have a greater potential for significant QT prolongation (i.e., gatifloxacin, moxifloxacin and sparfloxacin).
- Hypokalemia

Bedaquiline treatment must be discontinued if the patient develops clinically significant ventricular arrhythmia. An additive or synergistic effect on QT prolongation of bedaquiline when co-administered with other medicinal products that prolong the QT interval cannot be excluded. Caution is recommended when using bedaquiline concomitantly with medicinal products with a known risk of QT prolongation. In the event that co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

In the MDR-TB treatment arm of the present study, moxifloxacin will be co-administered with bedaquiline. This is to prevent the development of resistance to the other drugs in the regimen in case the Subject's *M. Tb* strain is resistant to pyrazinamide. ECG assessments will be performed on all Subjects at baseline, each treatment visit and during the follow-up visit on Day 70.

Hepatic safety

Increases in transaminases were seen in clinical trials during administration of bedaquiline with the background regimen. Subjects should be monitored during treatment.

Other hepatotoxic medicinal products and alcohol should be avoided while taking bedaquiline, especially in Subjects with diminished hepatic reserve.

2.5.2. PA-824

In the thirteen clinical studies (9 Phase 1 and 4 Phase 2) completed to date, a total of 289 healthy volunteers (163 in Phase 1 studies conducted by TB Alliance and 126 in a thorough QT study conducted by the NIH) and 315 Subjects with TB have taken PA-824. Multiple dosing has extended for as long as 8 weeks. In montherapy EBA studies, PA-824 has been shown to have bactericidal activity and in efficacy studies of up to 8 weeks in duration, regimens containing PA-824 have demonstrated activity either better than, or at least as good as, the HRZE control regimen (studies NC001, NC002 and NC003). PA-824 is a new drug with a novel mechanism of action with no pre-existing resistance making it suitable to treat both DS- and MDR-TB. It also has the potential, when used as part of a multi-drug regimen, to shorten the duration of treatment for TB. 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

Cataracts

While the detailed examinations in Phase 2 have not raised concern for humans, ophthalmologic examinations, with slit lamp exam and grading of lens opacities, will continue in NC-005. These examinations are to follow up on the finding of cataracts in rats exposed to PA-824 in preclinical studies.

Testicular Toxicity

Although all clinical evaluations of potential testicular toxicity in NC-002 failed to demonstrate any effect, all male Subjects in NC-005 will have baseline and periodic assays done of follicular stimulating hormone (FSH) as a sensitive test of early testicular damage.

Central Nervous System

The PA-824 pre-clinical program identified potential CNS-related toxicities and one Subject treated with PA-824 in clinical study NC-002 experienced a seizure while on treatment. Close surveillance will be in place to identify any seizures or significant central nervous system (CNS) signs or symptoms during study NC-005.

Hepatic Safety

Hepatic enzyme increases have been seen in Subjects treated with PA-824 in combinations with various other medications during the clinical development program. It is difficult to assign specific causality to any one drug within a regimen; nonetheless, study NC-005 will include specific monitoring of hepatic enzymes.

2.5.3. Pyrazinamide

Pyrazinamide (Z) is a standard drug used as part of the four drug HRZE regimen used for the first two months of intensive therapy for drug-sensitive TB as recommended by the WHO and many National TB programs. Please see the Package Insert [42] for more detail. Z is active against TB *in vitro* and it potentiates the bactericidal and sterilizing activity of both bedaquiline and PA-824 in mouse models of TB infection [12,13,23]. Pyrazinamide enhanced the bactericidal activity of both bedaquiline and PA-824 in Study NC-001-(J-M-Pa-Z) as noted by decreases over 14 days in the CFU counts in sputum among Subjects.

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 [42].

2.5.4. Moxifloxacin

Moxifloxacin is currently marketed globally for a variety of acute infectious diseases and has been studied for the treatment of tuberculosis in multiple clinical studies. The inclusion of moxifloxacin in a novel regimen (PA-M-Z) to treat both DS and MDR-TB has resulted in bactericidal activity in both 14 day and 8 week efficacy studies. Furthermore, moxifloxacin is currently used as a second-line agent to treat MDR-TB and in this study it will be used as a component of the regimen used in the MDR-TB treatment arm. The following list of known and potential risks is based on the warnings and precautions and adverse reactions sections of the current package label [37].

Warnings and Precautions

- Increased risk of tendinitis and tendon rupture. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroids, and in patients with kidney, heart or lung transplants. Discontinue if pain or inflammation in a tendon occurs.
- Prolongation of the QT interval and isolated cases of torsade de pointes has been reported. Avoid use in patients with known prolongation, hypokalemia, and with drugs that prolong the QT interval. Use caution in patients with proarrhythmic conditions such as clinically significant bradycardia or acute myocardial ischemia.
- Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. Discontinue drug use at first sign of skin rash, jaundice or any other sign of hypersensitivity.
- Central nervous system (CNS) events including dizziness, confusion, hallucination, depression, and rarely suicidal thoughts or acts may occur after first dose. Use caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold.
- *Clostridium difficile*-associated diarrhea: Evaluate if diarrhea occurs.
- Peripheral neuropathy: Discontinue if symptoms occur.

Adverse reactions

Most common reactions (≥3%) were nausea, diarrhea, headache, and dizziness.

2.6. Overall Benefit/Risk Assessment

Subjects in this study will be given regimens for 56 days that are not fully proven for the long term treatment of pulmonary TB. However these drugs, individually and in combination are known to have anti-tuberculosis activity and a delay of treatment with the full standard regimen of 56 days is not expected to have an adverse impact on the ultimate cure of TB in these Subjects. Subjects in this study will have their TB infection carefully characterized, with drug sensitivity profiles established, and they will receive treatment with study drugs that have demonstrated activity against *M. Tb*. Subjects will receive individualized medical attention; this will allow a continuous monitoring of the health conditions of each Subject, any of whom can be withdrawn at any stage of the trial and removed from study treatment should his/her condition suggest to the Investigator that this would be in his/her best interest. Multiple blood samples will be taken for safety laboratory studies, and ECGs will be taken at multiple time points. One concern in particular, combining two agents with known QT-prolonging effects (bedaquiline and moxifloxacin), has been addressed specifically by carefully identifying and excluding subjects with risk factors that might predispose them to cardiac arrhythmias, screening all subjects for evidence of existing cardiac disease and monitoring all subjects with ECGs throughout the study.

The regimens to be tested in this study have all demonstrated efficacy in the treatment of pulmonary tuberculosis in non-clinical and clinical studies. Specifically, the regimen J-Pa-Z was generally well-tolerated and demonstrated bactericidal activity in a 14 day EBA study. The potential risks associated with the study drugs and regimen has been identified and will be monitored carefully throughout the conduct of the study.

3. TRIAL RATIONALE AND OBJECTIVES

3.1. Trial Rationale

This trial seeks to establish the anti-tuberculosis effect (bactericidal activity (BA)) of the study drugs on serial TTP of *M.Tb* in sputum over 56 days (8 weeks) of therapy. The combinations of drugs in this study have all demonstrated good microbicidal and sterilizing activity in mouse models of TB infection and a 14 day EBA study and this study will determine the effects of these combinations in patients with DS and MDR-TB over 56

days. These regimens have the potential to substantially shorten the current duration of regimens for both DS and MDR-TB.

3.2. Study Design Rationale

This study will be a 56 day BA design incorporating 4 parallel treatment groups. This design allows comparison of the results of this study with similar prior studies of treatments for TB. The study will be open label, as the primary endpoint related to TTP is objective and will therefore not be subject to bias. The mycobacteriology laboratory personnel will remain blinded to the study arm assignment until closure of the BA results. All Subjects who undergo randomization (DS-TB treatment arms) or assignment (MDR-TB treatment arm) will be selected according to the study inclusion and exclusion criteria thereby ensuring that all Subjects are appropriate for inclusion in any of the 4 treatment arms. No placebo treatment is included in this study – all Subjects will be given either active study treatment or HRZE control. Given the availability of effective treatment for TB, and the serious consequences of allowing TB to go untreated, inclusion of a placebo treatment arm would be unethical.

Upon treatment completion, the DS-TB Subjects will be given sufficient doses of standard of care TB treatment, as appropriate, to cover the time period from attending their last visit at the study clinic until their scheduled visit at the TB clinic. All Subjects will immediately be referred to the National TB Treatment Program local TB clinic.

3.3. Dose Rationale

3.3.1. Bedaquiline

In one of the experimental treatment arms ($J_{(\text{loading dose/t.i.w.})}$PaZ), bedaquiline will be administered at the MDR-TB registered dose (i.e. registered in some countries) of 400mg once daily for Days 1-14 followed by 200mg three times per week for Days 15-56. In another experimental treatment arm ($J_{(200\text{mg daily})}$PaZ), bedaquiline will be administered at 200mg once daily for Days 1-56 in order to compare the efficacy and safety of these two dosing schemes. The two week loading dose followed by a t.i.w dose has been shown to be an effective treatment for MDR-TB, but is complex and difficult to administer in standard TB treatment clinics. By administering bedaquiline at a fixed daily dose of 200mg, the overall exposure to the drug over a 3- or 4-month regimen will not be substantially greater than if it were administered using the loading dose/t.i.w dosing scheme over 6 months, and should provide similar efficacy and safety. Over the course of this 8 week study, Subjects in the $J_{(\text{loading dose/t.i.w.})}$ arm will receive a total cumulative dose of 9.2 gm while Subjects in the $J_{(200\text{mg daily})}$ arm will receive a total of 11.2 gm. However, based on PK modeling, the highest Cmax and AUC exposures will occur in the $J_{(\text{loading dose/t.i.w.})}$ arm at the end of the first 2 weeks of dosing. Given that the Subjects in the $J_{(200\text{mg daily})}$ arm will never achieve exposures greater than those in the $J_{(\text{loading dose/t.i.w.})}$ arm, yet will receive slightly more total drug, it is likely that the daily dosing scheme will not result in increased tolerability or safety problems and will achieve good anti-tuberculosis activity. As this is a clinical trial, the Subjects will be closely monitored for safety and improvement/worsening of their underlying TB disease.

3.3.2. PA-824

PA-824 has demonstrated good microbicidal activity at the 200mg daily dose as monotherapy in studies PA-824-CL-007 and PA-824-CL-010, in combination with either bedaquiline or pyrazinamide over 14 days in the EBA Study NC-001-(J-M-Pa-Z) and in combination with either bedaquiline and/or pyrazinamide and/or clofazimine over 14 days in the EBA Study NC-003-(C-J-Pa-Z). In the EBA Study PA-824-CL-010 the 100mg dose demonstrated similar microbicidal activity to the 150 and the 200mg daily dose over 14 days. However because sterilizing relapse-free cure of TB may ultimately require a regimen with higher drug exposures, the 200mg dose has been chosen for this study.

3.3.3. Moxifloxacin

The standard dose of moxifloxacin for a multitude of indications is 400mg daily. This is the dose that has been studied in clinical studies NC-001 and NC-002 and is the dose of moxifloxacin in the on-going REMox TB study.

3.3.4. Pyrazinamide

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. 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 [43].

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 1500mg 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 1500mg 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 1500mg dose.

Pyrazinamide has demonstrated microbicidal activity at the 1500mg daily dose as monotherapy and in combination with either bedaquiline and/or PA-824 and/or clofazimine over 14 days in the EBA Study NC-003-(C-J-Pa-Z). As described above, the combination J-PA-Z, with Z dosed at a fixed dose of 1500mg daily, demonstrated good efficacy in this study. Furthermore, study NC002 included two arms containing the 1500mg fixed daily dose of pyrazinamide ($PA_{(100)}$-M-Z and $PA_{(200)}$-M-Z), both of which demonstrated good efficacy compared to the HRZE control with pyrazinamide dosed using the standard weight-banding. In the NC002 study, both arms containing pyrazinamide dosed at the 1500mg fixed dose were generally well-tolerated with no increase in the number of subjects with significant increases ($\geq$5X ULN) in hepatic enzyme elevations. Taken together, these studies confirm the PK model results – that a daily, fixed pyrazinamide dose of 1500mg offers equal efficacy and no significant increase in hepatotoxicity.

3.3.5. HRZE Combination Tablets

HRZE combination tablets will be used at standard weight-adjusted doses.

3.4. Trial Objectives

The primary objective of this study is to evaluate the bactericidal activity, safety, and tolerability of J-Pa-Z in drug-sensitive TB and J-M-Pa-Z in MDR TB. Secondary objectives include evaluating the bactericidal activity, safety and tolerability of bedaquiline dosed using two different schemes (the loading dose/t.i.w schedule and 200mg a day). Additional key secondary objectives are to evaluate the population PK characteristics of J, M, Pa and Z when administered as a part of 3- and 4-drug regimens in adults with TB, and investigation of the methodology of sputum sampling by comparing CFU counts and TTP results, quantified from both Coached Spot Sputum and Overnight Sputum samples.

4. TRIAL DESIGN

4.1. Summary

This is a Phase 2, multi-center, open-label, partially randomized clinical trial in four parallel treatment groups. The trial will be performed at multiple centres globally. Specific sites will be identified to enrol MDR-TB Subjects and/or take part in the PK sub-study.

A total of approximately 240 male and female, newly diagnosed Subjects with drug-sensitive or multi drug-resistant, smear positive pulmonary tuberculosis aged 18 to 75 years (inclusive) will be enrolled. A total of 180 DS-TB Subjects (60 per treatment arm) will be randomized. Up to 60 MDR-TB Subjects will be assigned. In the event of the DS-TB treatment arms being fully recruited (i.e. 60 Subjects in each of the three treatment arms) before the MDR-TB treatment arm has enrolled 60 Subjects, the Sponsor may elect to close the study for all treatment arms, or close the DS-TB treatment arms and continue the study with MDR-TB recruitment while analyzing the DS-TB data.

All Subjects will have up to a maximum of 9 days screening, receive 8 weeks of treatment, and have follow-up visits performed at 2 and 12 weeks after study treatment completion with Telephonic Survival Follow Up for survival data at 6 (Month 8), 12 (Month 14), 18 (Month 20) and 24 months (Month 26) after completion of IMP. Subjects who withdraw after $\leq$ 14 days of IMP should attend a follow-up visit 2 weeks after the last dose of IMP, while Subjects who withdraw after $\geq$ 15 days of IMP should complete all the scheduled Follow Up.

Subjects with Drug-Sensitive (DS) TB will be randomized to receive:

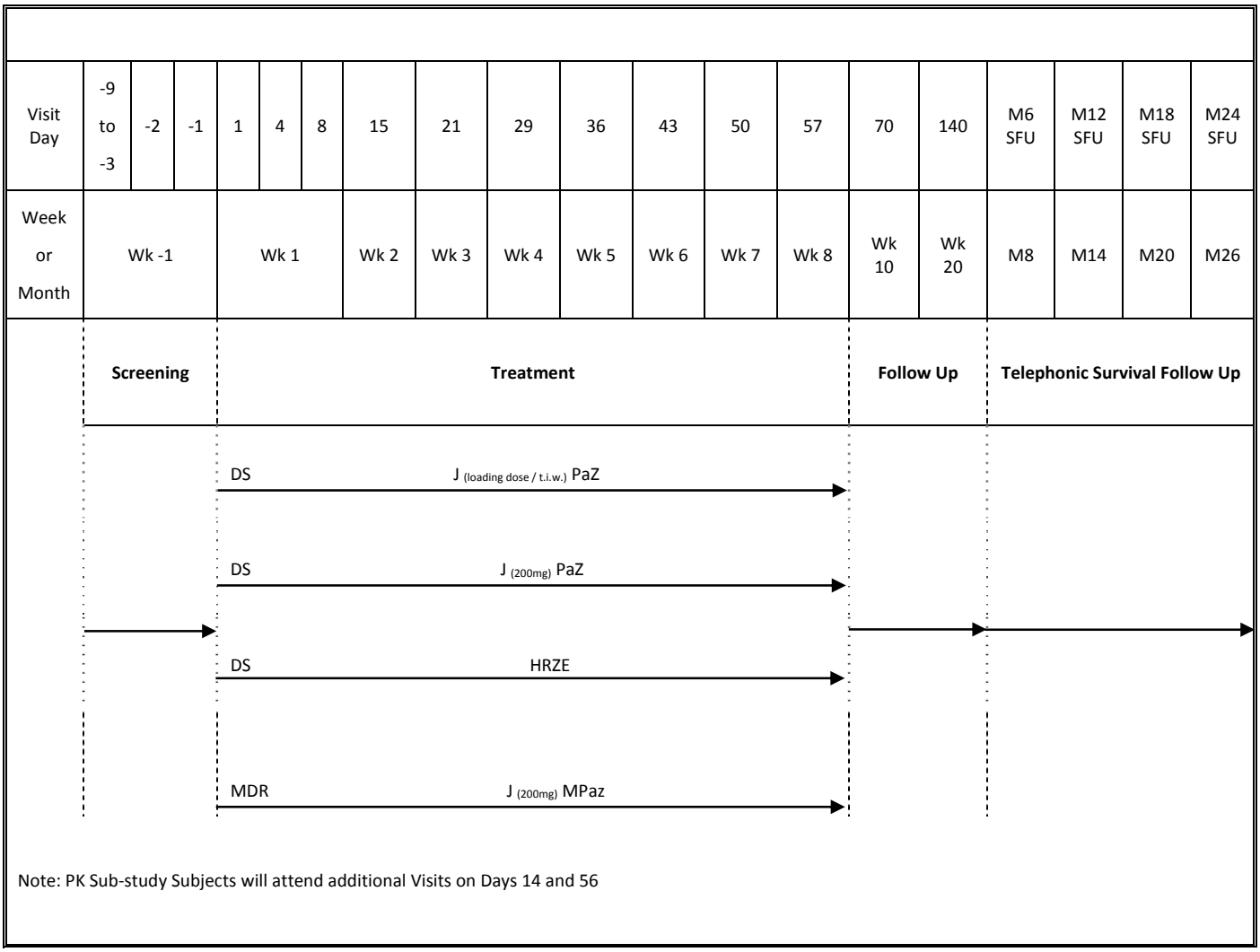
- $J_{(\text{loading dose/t.i.w.})}$PaZ or
- $J_{(200mg)}$PaZ or
- HRZE

Subjects with Multi Drug-Resistant (MDR) TB will receive:

- $J_{(200mg)}$MPaZ

The HRZE treatment arm is included as a control for the drug-sensitive treatments (both efficacy and safety assessments) and the quantitative laboratory mycobacteriology testing.

Figure 1: Trial Schematic



Note: PK Sub-study Subjects will attend additional Visits on Days 14 and 56

4.2. Trial Endpoints

The Overnight Sputum Samples will be used to determine the primary outcome of the study.

4.2.1. Primary Endpoint

The Bactericidal Activity (BA_{TTP}(0-56)) as determined by the rate of change in time to sputum culture positivity (TTP) over 8 weeks of treatment in the Mycobacterial Growth Indicator Tube system, represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time.

4.2.2. Secondary Endpoints

4.2.2.1. Efficacy:

- The BA_{TTP}(0-2) and BA_{TTP}(14-56) as determined by the rate of change in time to sputum culture positivity (TTP) over Days 0 to 2, and Days 14 to 56 treatment, represented by the model-fitted log(TTP) as calculated by the regression of the observed log(TTP) counts over time.
- The BA_{CFU}(0-56), BA_{CFU}(0-2) and BA_{CFU}(14-56) as determined by the rate of change in colony forming units (CFU) over 8 weeks of treatment represented by the model-fitted log(CFU) results as calculated by the regression of the observed log(CFU) results over time.

- Time to sputum culture conversion using data from weekly cultures through 8 weeks of treatment (separately, on solid and liquid media).
- Proportion of Subjects with sputum culture conversion at 4, 6 and 8 weeks (separately, on solid and liquid media).
- The BA_{CFU}(0-56, 0-2 and 14-56) and BA_{TTP}(0-56, 0-2 and 14-56) of $J_{(loading\ dose/t.i.w.)}$PaZ compared to $J_{(200mg)}$PaZ from DS-TB treatment arms.
- Investigation of the methodology of sputum sampling by comparing CFU counts and TTP results, each quantified in both Coached Spot Sputum and Overnight Sputum samples; however Overnight Sputum Samples are considered the reference samples.

4.2.2.2. Safety and Tolerability:

- Incidence of Treatment Emergent Adverse Events (TEAEs) will be presented by severity (DMID Grade), drug relatedness and seriousness, leading to early withdrawal and leading to death, by group.
- Quantitative and qualitative clinical laboratory result measurements, including observed and change from baseline will be presented and summarized by group.
- 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 also be categorized and presented, by group.
- Descriptive statistics will be presented for ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2] lens opacity classification and grading) and listed by Subject. Categorical data for lens opacity will be summarized in a frequency table for the left and right eye, respectively, including change from baseline, and summarized by group.
- Descriptive statistics will be presented for serum FSH measurements (mean and median at baseline, 4, 8 and 10 weeks and mean change from baseline at 4, 8 and 10 weeks) by group.
- Other safety variables will be presented by group and listed by Subject.

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

4.2.2.3. Pharmacokinetics / Pharmacokinetics-Pharmacodynamics (PK-PD):

Pharmacokinetics will consist of two separate schedules:

- *All Subjects:*

  Pre-dose sampling at Days 1, 4, 8, 15, 22, 29, 36, 43, 50 and during the site visit on Days 57 and 70 to measure C_{trough} levels of J, J metabolite M2, M, Pa and Z as per the table below.

- *PK Sub-study Subjects:*

  In addition to the general PK samples, there will be intense PK sampling on Days 14 and 56 at pre-dose, 1, 2, 4, 8 and 24 hours after dosing in a sub-group of 15 Subjects in each treatment arm across selected sites.

Pharmacokinetic Analysis:

All measured PK concentrations will be listed.

For the C_{trough} samples, only descriptive statistics will be prepared (average C_{trough}) derived for each analyte on Days 4, 8, 15, 22, 29, 36, 43, 50, 57 and 70 as follows:

Table 8 : PK Analyte/s Per Treatment Arm

Treatment Arm	Analyte/s	Subject Population
$J_{(loading\ dose/t.i.w.)}$PaZ	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}$PaZ	J, J metabolite M2, Pa, Z	DS-TB

$J_{(200mg)}$MPaZ	J, J metabolite M2, M, Pa, Z	MDR-TB
HRZE	Z	DS-TB

For the PK sub-study samples, the following PK parameters will be estimated from the individual (per Subject) PK plasma concentrations: minimum observed PK plasma concentration (C_{min}), maximum observed PK plasma concentration(C_{max}), time to reach C_{max} obtained without interpolation (T_{max}), area under the PK plasma concentration time (t) curve from zero to the last quantifiable PK plasma concentration prior to the subsequent dose, using the linear trapezoidal rule ($AUC_{(0-t)}$), area under the PK plasma concentration time (t) curve from zero to 24 hours ($AUC_{(0-24)}$). These will be derived for each analyte, on Days 14 and 56, as follows:

Table 9 : PK Analyte/s Per Treatment Arm

Treatment Arm	Analyte/s	Subject Population
$J_{(loading\ dose/t.i.w.)}$PaZ	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}$PaZ	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}$MPaZ	J, J metabolite M2, M, Pa, Z	MDR-TB
HRZE	Z	DS-TB

$J_{(200mg)}$PaZ compared to $J_{(loading\ dose/t.i.w.)}$PaZ and $J_{(200mg)}$MPaZ :

In order to compare the effects of the two J dosing schemes on bedaquiline exposure, the C_{max}, C_{min} and AUC of J and M2 will be compared using PK sub-study data from days 14 and 56 from the $J_{(loading\ dose/t.i.w.)}$PaZ and $J_{(200mg)}$PaZ DS-TB arms. A secondary comparison of the PK parameters from the sub-study parameters of J and M2 between the $J_{(200mg)}$PaZ DS-TB and $J_{(200mg)}$MPaZ MDR-TB arms will also be performed.

Another comparison of J and M2 exposure will be performed using the C_{trough} data from the $J_{(loading\ dose/t.i.w.)}$PaZ and $J_{(200mg)}$PaZ DS-TB arms, with a secondary comparison between the $J_{(200mg)}$PaZ DS-TB and $J_{(200mg)}$MPaZ MDR arms.

Pharmacokinetics-Pharmacodynamics (PK-PD):

Pearson correlation coefficients will be reported for the correlation analysis of all relevant PK-PD and exploratory PK-PD endpoints.

Descriptive summary statistics for TMIC will be presented.

Exploratory PK-PD Endpoints:

- Correlations between C_{trough} plasma drug concentrations, efficacy and safety findings will be performed in an exploratory fashion.
- Comparison of TMIC (based on data from the PK sub-study parameters) for J between $J_{(loading\ dose/t.i.w.)}$PaZ and $J_{(200mg)}$PaZ in DS-TB treatment arms.
- Correlations between plasma drug concentrations and efficacy and safety findings will be performed in an exploratory fashion, as follows:

  BA_{TTP}(0-56) and BA_{TTP}(14-56) versus the following PK variables (at Day 14 and Day 56) will be presented for J, Pa and M:

  - C_{max}
  - AUC(0-24)
  - Time over Minimum inhibitory concentration (TMIC) of J, Pa and M, both with and without taking protein binding shift into account.

4.2.2.4. Exploratory Endpoints:

- Sub-analysis of the primary and secondary efficacy endpoints of the MDR-TB pyrazinamide resistant Subjects compared to the MDR-TB sensitive Subjects.
- Sub-analysis of the primary and secondary efficacy endpoints of the H or R mono-resistant Subjects will be evaluated as separate sub-groups.

4.2.2.5. General Mycobacteriology:

Overnight Sputum and Coached Spot Sputum Samples will be obtained at all scheduled visits, except the Screening Visit when only a Coached Spot Sputum Sample will be collected. Sputum samples will not be collected at Early Withdrawal Visits. Cultures will be grown from all Overnight Sputum and Coached Spot Sputum Samples collected from Day -2 onwards. The Overnight Sputum Samples will be considered the reference samples.

The following mycobacteriology assays will be carried out:

Table 10 : General Mycobacteriology

Sample	Type	Assessments	Comments
Screening	Coached Spot Sputum Sample	• Direct microscopy for acid-fast bacilli • Molecular assay for identification of *M. Tb* and drug susceptibility (such as GeneXpert or MTBDR*plus*) to confirm the diagnosis of TB and distinguish between DS-TB and MDR-TB • Molecular test for fluoroquinolone resistance (such as MTBDR*sl*) for MDR-TB Subjects to establish susceptibility to moxifloxacin	All to be performed at the Trial Appointed Laboratory.
Baseline Overnight Sputum Samples named Day -2 and -1	Overnight Sputum Sample	• Direct microscopy for acid-fast bacilli • Molecular / antigen test to confirm *M. Tb* • Culture: MGIT and Solid Media (quantitative for CFU) • DST: SIRE, Z • MIC: J, Pa, M • DNA for pncA Sequencing	Z DST resistance must be repeated to confirm.
Baseline Coached Spot Sputum Samples named Day -2 and -1	Coached Spot Sputum Sample	• Culture: MGIT and Solid Media (quantitative for CFU)	For determination of logCFU and logTTP rates of change for comparison to cultures from Overnight Sputum Sample.

Sample	Type	Assessments	Comments
Overnight Sputum Samples named Days 1, 3, 7, 14, 21, 28, 35, 42, 49 and 56	Overnight Sputum Sample	• Culture: MGIT and Solid Media (quantitative for CFU) • The last positive sample from withdrawn Subjects who have not converted to culture negative status OR Subjects who are still culture positive at 8 weeks OR the first positive sample after conversion to culture negative status for subjects who have 'relapsed'*****: o DST: SIRE, Z o MIC: J, Pa, M	
Coached Spot Sputum Samples named Days 1, 3, 7, 14, 21, 28, 35, 42, 49, and 56	Coached Spot Sputum Sample	• Culture: MGIT and Solid Media (quantitative for CFU)	For determination of logCFU and logTTP rates of change for comparison to cultures from Overnight Sputum Sample.

- The above assays will be carried out according to procedures described in the Laboratory Manual.
- The Coached Spot Sputum Sample can be used for all assays, except CFU and TTP, if results cannot be obtained from the Overnight Sputum Sample.
- pncA sequencing and MIC isolates can be batched at the end of the study.
- *****If the Subject was treated with study medication for less than 9 days, the mycobacteriology testing will be performed on the Day -2 sample isolate only.
- *****Culture negativity is defined as the first of two consecutive negative cultures, except for the week 8 time point, where a singular negative is acceptable.

4.3. Trial Population

4.3.1. Inclusion Criteria

Subjects are required to meet all of the following inclusion criteria in order to be randomized.

1. Provide written, informed consent prior to all trial-related procedures. Male or female, aged between 18 and 75 years inclusive.
2. Body weight (in light clothing and with no shoes) between 35 and 100 kg, inclusive.
3. Tested at the trial appointed laboratory: *M. Tb* positive on molecular test (e.g. GeneXpert or Hain) and sputum smear-positive pulmonary TB on direct microscopy for acid-fast bacilli (at least 1+ on the IUATLD/WHO scale (Appendix 1)).
   For DS-TB treatment arms (defined as sensitive to rifampicin based on molecular sensitivity testing), Subjects should be:
   a. either newly diagnosed or untreated for at least 3 years after cure from a previous episode (Subject can give a history of cure and previous treatment); AND
   b. Previous TB treatment must be discontinued as per exclusion criteria 16.

   For MDR-TB treatment arm (defined as resistant to rifampicin based on molecular sensitivity testing), Subjects should be:
   a. sensitive to moxifloxacin by molecular sensitivity testing; AND

b. either newly diagnosed or could have previously been treated for DS-TB and/or MDR-TB (≤ 7 days of treatment). Previous MDR-TB treatment must be discontinued as per exclusion criteria 17.

4. A chest X-ray picture which in the opinion of the Investigator is compatible with TB.
5. Ability to produce an adequate volume of sputum as estimated from a screening Coached Spot Sputum Sample assessment (estimated 10 ml or more overnight production).
6. Be of non-childbearing potential or using effective methods of birth control, as defined below:

Non-childbearing potential:

a. Subject - not heterosexually active or practises sexual abstinence; or
b. Female Subject/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/sexual partner - vasectomised or has had a bilateral orchidectomy minimally three months prior to screening.

Effective birth control methods:

A double contraceptive method should be used as follows:

a. Double barrier method which can include any 2 of the following: a male condom, diaphragm, cervical cap, or female condom (male and female condoms should not be used together); or
b. Barrier method (one of the above) combined with hormone-based contraceptives or an intra-uterine device for the female Subject/partner;

and are willing to continue practicing birth control methods throughout treatment and for 6 months (both male and female Subjects) after the last dose of study medication or discontinuation from study 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 or female partners of male Subjects to prevent pregnancy).

4.3.2. Exclusion Criteria

Subjects will be excluded from participation if they meet any of the following criteria.
Medical Criteria

1. Evidence of clinically significant (as judged by the Investigator), metabolic, gastrointestinal, cardiovascular, musculoskeletal, ophthalmological, pulmonary, neurological, psychiatric or endocrine diseases, malignancy, or other abnormalities (other than the indication being studied) including malaria. A rapid test for malaria may be carried out if indicated.
2. Karnofsky performance status score of < 60% (Appendix 4).
3. Poor general condition where any delay in treatment cannot be tolerated per discretion of the Investigator.
4. Clinically significant evidence of extrathoracic TB (e.g. miliary TB, abdominal TB, urogenital TB, osteoarthritic TB, TB meningitis), as judged by the Investigator.
5. History of allergy or hypersensitivity to any of the study Investigational Medicinal Products or related substances.
6. Known or suspected current alcohol and/or drug abuse (positive urine drug screen) or history thereof within the past 2 years that is, in the opinion of the Investigator, sufficient to compromise the safety and/or cooperation of the Subject.
7. For HIV infected Subjects:
    a. having a CD4+ count <100 cells/µL;
    b. with an AIDS-defining opportunistic infection or malignancies (except pulmonary TB);

c. currently treated with or will need to initiate antiretroviral therapy (ART) which is not compatible with the allowed ARTs and is not considered an appropriate candidate for switching to a regimen of ARVs which is allowed as follows:
    - Triple nucleoside reverse transcriptase inhibitor (NRTI) based regimen consisting of zidovudine, lamivudine, and abacavir;
    - Nevirapine based regimen consisting of nevirapine in combination with any NRTIs;
    - Lopinavir/ritonavir (Aluvia™) based regimen consisting of lopinavir/ritonavir (Aluvia™) in combination with any NRTIs;
    - Raltegravir in combination with nucleoside reverse transcriptase inhibitors (NRTIs);

d. cannot ensure a 2 week interval between commencing IMP and the start of ART.

8. Having participated in other clinical study/ies with investigational agent/s within 8 weeks prior to trial start.
9. Significant cardiac arrhythmia requiring medication.
10. Subjects with the following at screening (per measurements and reading done by Central ECG):
    a. Marked prolongation of QT/QTc interval, e.g. confirmed demonstration of QTcF (Fridericia correction) or QTcB (Bazett correction) interval >450 ms at screening;
    b. History of additional risk factors for Torsade de Pointes, e.g. heart failure, hypokalemia, family history of Long QT Syndrome;
    c. Use of concomitant medications that are known to prolong the QT/QTc interval (see exclusion criteria 19 as well as list of restricted medication in Section 4.8.1);
    d. Any clinically significant, in the opinion of the Investigator, ECG abnormality.
11. Females who are pregnant, breast-feeding, or planning to conceive a child during the study or within 6 months of cessation of treatment. Males planning to conceive a child during the study or within 6 months of cessation of treatment.
12. Diabetes Mellitus resulting in hospitalization in the past year.
13. Evidence of lens opacity on slit lamp ophthalmologic examination as defined by a grading of >1+ on the AREDS2 grading system.
14. For males, any history of a clinically significant abnormality in the reproductive system.

Specific Treatments

15. Previously received treatment with PA-824, bedaquiline or moxifloxacin as part of a clinical trial.
16. For the DS-TB treatment arms: treatment with any drug active against *M. Tb* within the 3 years prior to Day 1 (including but not limited to isoniazid, ethambutol, amikacin, bedaquiline, clofazimine, cycloserine, fluoroquinolones, rifabutin, rifampicin, streptomycin, kanamycin, para-aminosalicylic acid, rifapentine, pyrazinamide, thioacetazone, capreomycin, thioamides, metronidazole). Exceptions include the use of fluoroquinolones and metronidazole as short-term treatment (≤2 weeks) for Non-*M.Tb* infections. Treatment should have been discontinued at least 3 months prior to Day 1. 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.
17. MDR-TB Subjects may have previously been treated for DS-TB with first-line TB drugs (isoniazid, rifampicin, ethambutol, pyrazinamide and/or streptomycin) and/or received ≤ 7 days MDR-TB treatment, provided that treatment is/was discontinued at least 7 days prior to randomization. It should be confirmed that the MDR-TB treatment can be safely stopped and the screening period is long enough to allow for a washout period of 5 times the longest half-life of the drugs.
18. 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 acute gout, allergy to any TB drug, their component or to the IMP.
19. Use of any drug within 30 days prior to dosing known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine). Exceptions may be made for Subjects that have received 3 days or less of one

of these drugs or substances, if there has been a wash-out period before administration of IMP equivalent to at least 5 half-lives of that drug or substance. Subjects who have taken drugs with long elimination half-lives such as amiodarone should be discussed with the Sponsor.

20. Use of any drugs or substances within 30 days prior to dosing known to be strong inhibitors or inducers of cytochrome P450 enzymes (including but not limited to quinidine, tyramine, ketoconazole, fluconazole, testosterone, quinine, gestodene, metyrapone, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafylline, cimetidine, dextromethorphan). Exceptions may be made for Subjects that have received 3 days or less of one of these drugs or substances, if there has been a wash-out period before administration of IMP equivalent to at least 5 half-lives of that drug or substance.
21. Any ARVs other than allowable ARVs detailed in exclusion criteria no. 7 above.

Based on Laboratory Abnormalities:

22. 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 2):
    a. serum magnesium and calcium (corrected for albumin) levels outside of the laboratory's reference range
    b. lipase grade 3 or greater (>2.0 x ULN);
    c. creatinine grade 2 or greater (>1.5 x ULN);
    d. hemoglobin grade 4 (<6.5 g/dL);
    e. platelets >grade 2 (under $50x10^9$ cells/L);
    f. serum potassium less than the lower limit of normal for the laboratory;
    g. aspartate aminotransferase (AST) grade 3 or greater (≥3.0 x ULN) to be excluded;
    h. alanine aminotransferase (ALT) grade 3 or greater (≥3.0 x ULN) to be excluded;
    i. 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;
    j. total bilirubin grade 3 or greater (≥2.0 x ULN, or ≥1.50 x ULN when accompanied by any increase in other liver function test) to be excluded, grade 2 (≥1.50 x ULN, or ≥1.25 x ULN when accompanied by any increase in other liver function test) must be discussed with and approved by the Sponsor Medical Monitor;

Any laboratory value which excludes the Subject may be repeated to confirm eligibility.
All inclusion and no 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, and receiving approval from the Sponsor Medical Monitor.

4.4. Treatment Plan: Schedule of Assessments

The trial consists of four periods, as follows:

- Screening Period (Day -9 to Day -1);
- Treatment Period (Day 1 to Day 57);
- Follow-Up Period (Day 70 to Day 140);
- Telephonic Survival Follow Up Contact at 6, 12, 18 and 24 months after last dose of IMP (Month 8, Month 14, Month 20 and Month 26).

Refer to:

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

4.4.1. Screening Period (Days -9 to Day -1)

- ***Naming of Overnight Sputum Samples for the Trial Period <u>Days -3 to Day 1</u>:*** The day Overnight Sputum Sample collection **<u>ends</u>** reflects the day to which that sample applies e.g. a sample where collection starts on Day -3 and ends on Day -2, is designated as the Day -2 Overnight Sputum Sample and results are also referred to as Day -2 results.
- ***Naming of Coached Spot Sputum Samples for the Trial Period <u>Days -9 to Day 1</u>:*** The Day -9 to -3 Coached Spot Sputum Sample/s will be named 'screen' (note, there is no matching Overnight Sputum Sample). The naming of Coached Spot Sputum Samples for Days -2, -1 and 1 will be designated as Day -2, -1 and 1 respectively and results are also referred to as Day -2, -1 and 1 results.

4.4.1.1. Day -9 to -3

Prior to this visit, Subjects must have a history of a positive molecular test (e.g. GeneXpert or Hain) or TB sputum smear microscopy result from their TB clinic or site of initial diagnosis.
The following information will be collected and procedures performed:

- Written Informed Consent (Main study, HIV testing and PK sub-study if applicable);
- Eligibility Assessment;
- Demographic Data;
- Medical and Treatment History;
- Single 12-lead ECG (the ECG should be done before any other assessments);
- Laboratory Safety Assessments (including serum FSH for male Subjects);
- Urine Pregnancy Test, (women of child bearing potential only, whether they are sexually active or not);
- HIV test and CD4 count; if an HIV test was performed within 1 month prior to trial start, it need not be repeated as long as documentation can be provided [ELISA and/or Western Blot]). Subjects may be on current antiretroviral therapy (ART) or commence ART during the study if required, provided there is at least a 2 week interval between commencing IMP and the start of ART. For ART which is allowed in conjunction with IMP please refer to section 4.8.1.2;
- Urine Drug Screen;
- Karnofsky Score;
- Tuberculosis Symptom Profile (TSP) Questionnaire;
- Chest X-ray (may be performed at Day -2 or -1 if not performed at Day -9 to -3 or if performed within 7 days prior to signing consent, the X-ray does not need to be repeated if the report and X-ray are available for review and interpretation);
- Vital Signs including weight;
- Physical Examination (full) including height;
- Ophthalmology Examination (may be performed at Day -2 or Day -1 if not performed at Day -9 to -3);
- Overnight Sputum Sample (starts +/- 4 pm on Day -3 ends on Day -2, named 'Day -2'), all isolates from positive cultures should be stored until study completion;
- Screening Coached Spot Sputum Sample (named 'screen');
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events.
- The screening visit (Day -9 to -3) may occur over a number of days i.e. all screening procedures do not have to be performed on the same day. All isolates from positive cultures should be stored until study completion.

4.4.1.2. Day -2

- If not already performed at Day -9 to -3:
  - Chest X-ray or if performed within 7 days prior to signing consent, the X-ray does not need to be repeated if the report and X-ray are available for review and interpretation;
  - Ophthalmologic Examination;
- Overnight Sputum Sample:
  - Day -2 ends – named 'Day -2'
  - Day -1 starts +/- 4 pm
  - all isolates from positive cultures should be stored until study completion;
- Coached Spot Sputum Sample (named 'Day -2'), all isolates from positive cultures should be stored until study completion;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse Events.

4.4.1.3. Day -1

The following information will be collected and procedures performed:

- Laboratory Safety Assessment: FSH only (male subjects);
- If not already performed at Day -9 to -3:
  - Chest X-ray or if performed within 7 days prior to signing consent, the X-ray does not need to be repeated if the report and X-ray are available for review and interpretation;
  - Ophthalmologic Examination;
- Vital Signs including weight;
- Randomization/Treatment Assignment;
- Overnight Sputum Sample
  - Day -1 ends – named 'Day -1'
  - Day 1 starts +- 4 pm
  - all isolates from positive cultures should be stored until study completion;
- Coached Spot Sputum Sample (named 'Day -1'), all isolates from positive cultures should be stored until study completion;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events.

4.4.2. Treatment Period (Day 1 to Day 57)

- **Hospitalization:**
  - Not required for study participation, however may be considered when necessary per local guidelines (e.g. for MDR-TB if required) and only for a limited period of time, after approval by the Sponsor on a case by case basis.
  - Subjects do not need to be hospitalized for the intensive PK sampling, but may remain as outpatients at the clinic for the applicable day, and return the following morning for their 24hour post dosing sample collection.

- **Investigational Medicinal Product (IMP) Administration:**
  - The Subject should be instructed to:
    - Take IMP orally once daily for 8 weeks (56 days), preferably around breakfast time, with a glass of water (approximately 240ml);
    - Subjects on the HRZE treatment arm <u>should not take IMP with a meal</u> (generally, no closer to meals than 1 hour before or 2 hours after a meal) and should take the Vitamin B6 supplement with the HRZE dose;

- Subjects on the bedaquiline containing arms should take IMP with a meal (generally allow the Subjects a window of 30 minutes before to 30 minutes after a meal);
- When Subjects return for clinic visits or are hospitalized, they will be dosed on site;
- **For the $J_{(loading\ dose/t.i.w.)}$ DS-TB treatment arm:** The bedaquiline dosing schedule is 400mg daily on days 1-14, and then 200mg 3x per week. The 3x per week doses must be given on the following specific days to accommodate the PK sampling: Days 15, 17, 20, 22, 24, 27, 29, 31, 34, 36, 38, 41, 43, 45, 48, 50, 53 and 56.

- **Overnight Sputum Sample:**
  - The Subject should be instructed to:
    - Collect the sample from approximately 4pm the afternoon prior to the visit and for approximately 16 hours overnight for each of the sampling days.
    - Collection must be finished prior to the administration of the next day's IMP, which will be administered at the study site.
  - ***Naming of Overnight Sputum Samples for the Trial Period Days -3 to Day 1:*** The day Overnight Sputum Sample collection ends reflects the day to which that sample applies e.g. a sample where collection starts on Day -3 and ends on Day -2, is designated as the Day -2 Overnight Sputum Sample and results are also referred to as Day -2 results.
  - ***Naming of Overnight Sputum Samples for the Trial Period Days 3 to 57:*** The day Overnight Sputum Sample starts reflects the day to which that sample applies e.g. a sample where collection starts on Day 3 and ends on Day 4, is designated as the Day 3 Overnight Sputum Sample and results are also referred to as Day 3 results.
  - The Coached Spot Sputum Sample can be used for all assays if results cannot be obtained from the Overnight Sputum Sample.
  - All isolates from positive cultures should be stored until study completion.
- **Coached Spot Sputum Collection:**
  - The Coached Spot Sputum Sample can be used for all assays, except CFU and TTP, if results cannot be obtained from the Overnight Sputum Sample.
  - ***Naming of Coached Spot Sputum Samples for the Trial Period Days -9 to Day 1:*** The Day -9 to -3 Coached Spot Sputum Sample/s will be named 'screen' (note, there is no matching Overnight Sputum Sample). The naming of Coached Spot Sputum Samples for Days -2, -1 and 1 will be designated as Day -2, -1 and 1 respectively and results are also referred to as Day -2, -1 and 1 results.
  - ***Naming of Coached Spot Sputum Samples for the Trial Period Days 3 to 57:*** The naming of Coached Spot Sputum Samples will match the naming of Overnight Sputum Samples for that period, i.e. the Coached Spot Sputum Sample collected on Visit Day 4 will be named Day 3 etc. and results are referred to as Day 3 results.
  - All isolates from positive cultures should be stored until study completion.
- **Timing of Assessments**
  - During the treatment period, all assessments must be done prior to dosing and the ECG must be completed before any laboratory or clinical procedures are carried out.
  - Laboratory Safety Assessments must be taken before IMP dosing.
  - Pharmacokinetics:
    - Pharmacokinetics will consist of two separate schedules:

      All Subjects:

      Pre-dose sampling at Days 1, 4, 8, 15, 22, 29, 36, 43, 50 and during the site visit on Days 57 and 70, to measure C_{trough} levels of J, J metabolite M2, M, Pa and Z as per Table 8.

      PK Sub-study Subjects:

In Addition to the general PK samples, there will be intense PK sampling on Days 14 and 56 at pre-dose, 1, 2, 4, 8 and 24 hours after dosing in a sub-group of 15 Subjects in each of the treatment arms across selected sites.

- Subjects do not need to be hospitalized for the PK sampling, but may remain as outpatients at the clinic for the applicable day and return the following morning for their 24 hour post dosing sample collection.
- PKs are to be collected at the specified time points within the allowed applicable window periods as follows: Pre-dose: 0-5 minutes before dose; 1-8 hours post-dose: +/- 5 minutes of dosing time; 24 hours post-dose: +/- 15 minutes of dosing time and prior to next dose.
- The site staff should attempt to take the PK samples at the same time of day for each timepoint.

- **Timing of Visits**
  - Up to and including Day 15 - No visit window (in order to accommodate PK sampling);
  - Day 14 must occur on Day 14, relative to Day 1 (in order to accommodate PK sampling for PK sub-study Subjects only);
  - Days 22 to 50 +/- 2 days;
  - Days 56 and 57 must occur on Days 56 and 57, relative to Day 1 (in order to accommodate PK sampling. The Day 56 visit is for PK sub-study Subjects only);
  - Day 70 (or 2 weeks after last dose of IMP in the case of early withdrawal) +/- 3 days;
  - Day 140 (or 12 weeks after last dose of IMP in the case of early withdrawal) +/- 14 days;
  - The 8, 14, 20 and 26 Month Telephonic Survival Follow Up Contact will be 6, 12, 18 and 24 months, respectively, after study treatment completion +/- 14 days;

Please Note : IMP dosing should not exceed 56 days even if visit windows are utilized;
: If a visit window is utilized, the next visit must be scheduled relative to Day 1.

4.4.2.1. Day 1

The following information will be collected and procedures performed <u>pre-dosing</u>:

- Eligibility Assessment;
- Triplicate 12-lead ECG (the ECG should be done before any other assessments);
- Laboratory Safety Assessments (excluding serum FSH);
- Pharmacokinetic sampling (pre-dose for all Subjects);
- Vital Signs including weight;
- Physical Examination (full);
- If not already performed at Day -1: Randomization/Treatment Assignment;
- Overnight Sputum Sample:
  - Day 1 ends, named ‘Day 1’
  - Subject given a sputum pot to start next Overnight Sputum Sample on Day 3
- Coached Spot Sputum Sample (named ‘Day 1’);
- Investigational Medicinal Product (IMP) Administration;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events.

4.4.2.2. Day 4

The following information will be collected and procedures performed pre-dosing:

- Pharmacokinetic sampling (pre-dose for all Subjects);
- Vital Signs including weight;
- Physical Examination (limited);
- Investigational Medicinal Product (IMP) Administration;

- Overnight Sputum Sample:
    - Day 3 ends, named 'Day 3';
    - Subject given a sputum pot to start next Overnight Sputum Sample on Day 7
- Coached Spot Sputum Sample (named 'Day 3');
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events.

4.4.2.3. Day 8; 22; 36 and 50 (+/- 2 days window for Visits on Days 22, 36 and 50)

The following information will be collected and procedures performed pre-dosing:

- Laboratory Safety Assessments (excluding serum FSH);
- Pharmacokinetic sampling (pre-dose for all Subjects);
- Vital Signs including weight;
- Physical Examination (limited);
- Investigational Medicinal Product (IMP) Administration;
- Overnight Sputum Sample:
    - Day 7 ends, named 'Day 7', Day 21 ends, named 'Day 21', Day 35 ends, named 'Day 35', Day 49 ends, named 'Day 49' respectively);
    - Subject given a sputum pot to start next Overnight Sputum Sample on the day preceding the next visit - excluding the Day 14 and 56 Visits;
- Coached Spot Sputum Sample Collection (named 'Day 7', 'Day 21', 'Day 35' and 'Day 49' respectively);
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events.

4.4.2.4. Day 14

- Intensive Pharmacokinetic Sub-study (for 15 Subjects in each treatment arm across selected sites) at pre-dose and 1, 2, 4, 8 and 24 hours after dosing;
- Investigational Medicinal Product (IMP) Administration;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events.

4.4.2.5. Day 15 and 43 (+/- 2 days window for Visit on Day 43)

The following information will be collected and procedures performed pre-dosing:

- Triplicate 12-lead ECG (the ECG should be done before any other assessments);
- Laboratory Safety Assessments (excluding serum FSH);
- Tuberculosis Symptom Profile (TSP) Questionnaire (performed on Day 15 only);
- Pharmacokinetic sampling (pre-dose for all Subjects);
- Vital Signs including weight;
- Physical Examination (limited);
- Investigational Medicinal Product (IMP) Administration;
- Overnight Sputum Sample:
    - Day 14 ends, named 'Day 14', Day 42 ends, named 'Day 42' respectively
    - Subject given a sputum pot to start next Overnight Sputum Sample on the day preceding the next visit;
- Coached Spot Sputum Sample (named 'Day 14' and 'Day 42' respectively);
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events.

4.4.2.6. Day 29 (+/- 2 days window)

The following information will be collected and procedures performed:

- Triplicate 12-lead ECG (pre-dose and 2 hours (± 15 minutes) post-dose, the ECG should be done before any other assessments);
- Laboratory Safety Assessments (including serum FSH for male Subjects);
- Urine Pregnancy Test, (women of child bearing potential only, whether they are sexually active or not);
- Tuberculosis Symptom Profile (TSP) Questionnaire;
- Pharmacokinetic Sampling (pre-dose for all Subjects);
- Vital Signs including weight;
- Physical Examination (limited);
- Investigational Medicinal Product (IMP) Administration;
- Overnight Sputum Sample:
    - Day 28 ends, named 'Day 28';
    - Subject given a sputum pot to start next Overnight Sputum Sample on the day preceding the next visit;
- Coached Spot Sputum Sample (named 'Day 28');
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events.

4.4.2.7. Day 56

- Intensive Pharmacokinetic Sub-study (for 15 Subjects from each treatment arm across selected sites) at pre-dose 1, 2, 4, 8 and 24 hours after dosing;
- Investigational Medicinal Product (IMP) Administration;
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events.

4.4.2.8. Day 57

The following information will be collected and procedures performed:

- Triplicate 12-lead ECG (the ECG should be done before any other assessments);
- Laboratory Safety Assessments (including serum FSH for male Subjects);
- Urine Pregnancy Test (women of child bearing potential only, whether they are sexually active or not);
- Tuberculosis Symptom Profile (TSP) Questionnaire;
- Pharmacokinetic Sampling (for all Subjects);
- Vital Signs including weight;
- Physical Examination (full);
- Overnight Sputum Sample ends (named 'Day 56');
- Coached Spot Sputum Sample (named 'Day 56');
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events;
- Referral to National TB Treatment Program.
  Upon treatment completion, the DS-TB Subjects will be provided with sufficient doses of standard of care TB treatment, as appropriate, to cover the time period from attending their last visit at the study clinic until their scheduled visit at the TB clinic. All DS-TB and MDR-TB Subjects will be referred to the local community TB clinics for standard anti-tuberculosis 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 study site staff to the clinic to determine if the Subject attended the clinic on the date as arranged.

4.4.2.9. Early Withdrawal

If the Investigator considers it necessary to withdraw a Subject from treatment or the study, this should be discussed with the Sponsor and their approval should be obtained. In case of early withdrawal during the treatment period of the study (prior to Day 56), 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:

- Triplicate 12-lead ECG (the ECG should be done before any other assessments);
- Laboratory Safety Assessments (including serum FSH for male Subjects);
- Urine Pregnancy Test (women of child bearing potential only, whether they are sexually active or not);
- Tuberculosis Symptom Profile (TSP) Questionnaire;
- Pharmacokinetic Sampling (all Subjects, pre-dose if IMP is administered);
- Vital Signs including weight;
- Physical Examination (full);
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events;
- Referral to National TB Treatment Program:
  Upon early withdrawal of IMP, the DS-TB Subjects will be provided with sufficient doses of standard of care TB treatment, as appropriate, to cover the time period from attending their last visit at the study clinic until their scheduled visit at the TB clinic. All DS-TB and MDR-TB Subjects will be referred to the local community TB clinics for standard anti-tuberculosis chemotherapy according to National 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 study site staff to the clinic to determine if the Subject attended the clinic on the date as arranged.

  Subjects who withdraw after $\leq$14 days of IMP administration are to return for the first follow-up visit (i.e. 2 weeks after last dose of IMP) only, while Subjects who withdraw after $\geq$15 days of IMP administration are to return for the first follow-up visit (2 weeks after last dose of IMP) and the second follow-up visit (12 weeks after last dose of IMP).

4.4.3. Follow-Up Period (Day 70 to Day 140)

4.4.3.1. Day 70 or 2 Weeks after Last Dose of IMP (+/- 3 days window)

The following information will be collected and procedures performed:

- Triplicate 12-lead ECG (the ECG should be done before any other assessments);
- Laboratory Safety Assessments (including serum FSH for male Subjects);
- Urine Pregnancy Test, (women of child bearing potential only, whether they are sexually active or not);
- Pharmacokinetic sampling (during the site visit for all Subjects);
- Vital Signs including weight;
- Physical Examination (limited);
- Concomitant Medication(s)/Other Treatment(s);
- Adverse events (all AEs and SAEs to be collected up to the end of the Day 70 Visit).

4.4.3.2. Day 140 or 12 Weeks after Last Dose of IMP (+/- 14 days window)

The following information will be collected and procedures performed pre-dosing:

- Urine Pregnancy Test, (women of child bearing potential only, whether they are sexually active or not);
- Ophthalmology Examination Day 140 or at least 90 days post the last dose of study medication;
- Adverse events (ophthalmologic AEs and all SAEs to be collected up to the end of the Day 140 Visit).

4.4.4. Telephonic Survival Follow Up Contact for Survival Data at 6, 12, 18 and 24 months after Last Dose of IMP (+/- 14 day window) i.e. Month 8, Month 14, Month 20 and Month 26

The following information will be collected during the telephonic follow-up:

- Establish and document whether the Subject remains alive or not;
- If the Subject has died, collect the date of death, cause of death and also if the death was related to TB or not.

4.5. Treatment Discontinuation and Subject Withdrawal

If the Investigator considers it necessary to withdraw a Subject from treatment or the study, this should be discussed with the Sponsor and their approval should be obtained. A Subject should immediately discontinue treatment and be prematurely withdrawn from the trial for the following reasons:

- Withdrawal of informed consent;
- Investigator considers that for safety reasons, it is in the best interest of the Subject that he/she be withdrawn;
- Specific Toxicities as described in section 7.3;
- Diagnosed with malaria during the treatment period. The Sponsor would recommend that Subjects who require treatment for malaria with drugs that have a potential of QTc prolongation should be withdrawn from study treatment and treated for malaria. Refer to Section 4.8.1.1 Recommendations for Concomitant use of Anti-Malarials;
- Serious Adverse Event (SAE);
- Pregnancy;
- At the specific request of the Sponsor or termination of the study by the Sponsor;
- Subject who, in the opinion of the Investigator or Sponsor, fails to comply with the Protocol.

Subjects (DS-TB and MDR-TB) who withdraw from the trial after having received IMP will not be replaced.
Upon discontinuation of IMP, the DS-TB Subjects will be provided with sufficient doses of standard of care TB treatment, as appropriate, to cover the time period from attending their last visit at the study clinic until their scheduled visit at the TB clinic. All DS-TB and MDR-TB Subjects will be referred to the local community TB clinics for standard anti-tuberculosis chemotherapy according to National 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 study site staff to the clinic to determine if the Subject attended the clinic on the date as arranged.
Any Subject who received at least one dose of IMP and is withdrawn or withdraws early from the study during the treatment phase will undergo an early withdrawal visit and will be requested to return for the applicable follow-up visits:

- Subjects who withdraw after 14 days or less of IMP administration are to return for the first follow-up visit (i.e. 2 weeks after last dose of IMP) only.
- Subjects who withdraw after $\geq$15 days of IMP administration are to complete all the scheduled Follow Ups (i.e. up to and including Month 26).

4.6. Stopping Rules

There are no trial specific stopping rules.
The trial or parts of the trial can be stopped by the Sponsor on advice from the Data Safety and Monitoring Committee (DSMC) after their review of applicable trial data. In addition, the Sponsor has the right to stop the trial or a specific Investigational Site at any time, although this should only occur after consultation between involved parties. Should this occur, the local and central Ethics Committee/Institutional review Board (EC/IRB) and Regulatory Authorities will be informed. Should the Trial/Investigational Site be closed prematurely, all trial materials (except documentation that has to remain stored at the Investigational Site) will be returned to the Sponsor or vendor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Subjects currently on treatment will receive an appropriate regimen and

all Subjects will be referred as soon as possible to the National TB Treatment Program in each participating country.

4.7. Subject Progress Definitions

4.7.1. Enrollment

- **Screening Failure**

Subjects from whom informed consent is obtained and documented in writing (that is, Subject signs an informed consent form), but who's not randomized/assigned to study treatment.

- **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 / assigned to treatment.

4.7.2. Completed Treatment

Subjects who complete the treatment visits through to the Day 57 visit.

4.7.3. Early Withdrawal

- During Treatment - Subjects who are assigned treatment and withdraw/are withdrawn from the trial prior to completion of treatment visits.
- During Follow-up - Subjects who are randomized / assigned to and complete treatment, however withdraw/are withdrawn from the trial prior to completion of all scheduled follow-up.

4.7.4. Completed Trial

- Subjects who are randomised / assigned to treatment and complete Treatment and Follow-Up.

4.8. Restrictions

4.8.1. Prior and Concomitant Medications and Other Treatments

Concomitant Medication is defined as any medication taken within 30 days prior to IMP administration or during the trial until Day 70. These, plus any other relevant treatment, will be recorded onto the electronic Case Report Form (eCRF).
Concomitant treatments should be kept to a minimum during the trial. However, if concomitant treatments are considered to be necessary for the Subject's welfare and are unlikely to interfere with the investigational medication, they may be given at the discretion of the Investigator. For any concomitant therapy given as a treatment for:

- An existing condition before signing of the informed consent form (ICF), the condition must be documented on the Medical History pages of the eCRF.
- A new condition or a worsening of an existing condition occurring after signing of the ICF, the condition must be documented on the Adverse Event pages of the eCRF.

The prescribing information for all concomitant 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 the HRZE and J-M-Pa-Z treatment arm: Any aluminium-containing antacids should be taken/administered at least one hour after the IMP dose.
- Subjects on the J-M-Pa-Z arm: antacids, sucralfate, multivitamins and other products containing multivalent cations, warfarin and didanosine are prohibited.

The following medicinal products are prohibited from Days -9 to -3 until after Day 57 or early withdrawal visit, unless part of study treatment:

- The systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolides such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 3 consecutive days;
- The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone);
- Medications of the statin class of compounds;
- Tricyclic antidepressants and related compounds, including amitriptyline, doxepin, desipramine, imipramine, clomipramine, cyclobenzaprine;
- Nonsedating antihistamines astemizole and terfenadine;
- The neuroleptics – phenothiazines, thioridazine, haloperidol, chlorpromazine, trifluoperazine, percyline, prochlorperazine, fluphenazine, sertindole and pimozide;
- The prokinetic cisapride;
- Quinoline antimalarials (e.g., chloroquine and quinacrine);
- Diuretics that deplete potassium;
- Medicinal products used to treat pulmonary TB (other than IMP): including but not limited to isoniazid, ethambutol, amikacin, bedaquiline, clofazimine, cycloserine, fluoroquinolones, rifabutin, rifampicin, streptomycin, kanamycin, para-aminosalicylic acid, rifapentine, pyrazinamide, thioacetazone, capreomycin, thioamides, metronidazole;
- Subjects may be treated with levofloxacin for a defined time period of <2 weeks, provided it was not given for TB and the diagnosis is known and documented.
- Use of any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).

4.8.1.1. Recommendations for Concomitant Use of Anti-Malarials

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

- Proguanil/atovaquone for $J_{(\text{loading dose/t.i.w.})}$PaZ, $J_{(200mg)}$PaZ or $J_{(200mg)}$MPaZ treatment arms (NOT for Subjects on the HRZE treatment arm);
- Artesunate plus sulfadoxine-pyrimethamine for the HRZE, $J_{(\text{loading dose/t.i.w.})}$PaZ, $J_{(200mg)}$PaZ or $J_{(200mg)}$MPaZ treatment arms.

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

4.8.1.2. Concomitant Use of Antiretroviral Therapy

For Subjects who are HIV positive, and are either taking or commencing ART, the following restrictions must be followed due to potential DDI with IMP:

- Antiretroviral therapy is prohibited except:
  - Triple nucleoside reverse transcriptase inhibitor (NRTI) based regimen consisting of zidovudine, lamivudine, and abacavir;
  - Nevirapine based regimen consisting of nevirapine in combination with any NRTIs;
  - Lopinavir/ritonavir (Aluvia™) based regimen consisting of lopinavir/ritonavir (Aluvia™) in combination with any NRTIs;

- Raltegravir (an integrase inhibitor) in combination with nucleoside reverse transcriptase inhibitors (NRTIs).

Subjects on all four treatment arms, who are commencing ART, may be entered onto the study provided there is at least a 2 week interval between commencing IMP and the start of ART.

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1. Trial Treatments

Subjects will receive oral, once-daily dosing for 8 weeks. Table 11 details the four treatment arms and their applicable Subject population.

Table 11 : Treatment Groups

Treatment Group		Subject Population
1.	• bedaquiline 400mg once daily Days 1-14, 200mg three times per week (2 x bedaquiline 100 mg tablets to be taken 3 times a week on specific study days as per section 5.3) Days 15-56; **plus** • PA-824 200mg once daily Days 1-56; **plus** • pyrazinamide 1500mg once daily Days 1-56.	DS-TB
2.	• bedaquiline 200mg once daily Days 1-56; **plus** • PA-824 200mg once daily Days 1-56; **plus** • pyrazinamide 1500mg once daily Days 1-56.	DS-TB
3.	• HRZE (isoniazid 75mg plus rifampicin 150mg plus pyrazinamide 400mg plus ethambutol 275mg combination tablets): Days 1-56 with the daily dose per the Subject's weight as follows: 30-37kg: 2 tablets; 38-54kg: 3 tablets; 55 – 70kg: 4 tablets; 71kg and over: 5 tablets. Vitamin B6 25mg one tablet daily Days 1-56 should be taken with the HRZE dose.	DS-TB
4.	• bedaquiline 200mg once daily Days 1-56; **plus** • moxifloxacin 400mg once daily Days 1-56; **plus** • PA-824 200mg once daily Days 1-56; **plus** • pyrazinamide 1500mg once daily Days 1-56.	MDR-TB

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 -9 to Day -3 and will be identified by a study generated Subject identification code for anonymity (Subject number). Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized per their DS- or MDR-TB status, and assigned a treatment number once all of the screening results are available.

The Investigational Medicinal Product will be centrally randomized by persons not directly involved with the trial. All treatment arms are open-label. Subjects, study Investigators and staff, site pharmacists/dispensers, including laboratory staff, sponsor staff and applicable CROs will know what treatment a Subject is randomized to receive. A treatment pack will be available for each Subject which will be identified by a treatment number.

In order to ensure there is no bias in treatment assignment, the study medication will be retained by the site pharmacist/registered dispenser. The person responsible for assigning study treatment will not be directly involved in Subject care responsibilities.

On initial randomization the site will request the site pharmacist/registered dispenser to assign an IMP treatment pack to the Subject dependent on their DS- or MDR-TB status (refer to Table 12). The site pharmacist/registered dispenser will assign to the Subject the next available applicable treatment pack, in a sequential basis starting from the lowest unused treatment number.

This process will be fully documented. Randomization/assignment by the pharmacist/registered dispenser may occur once all the screening results are available and the Investigator has determined that the Subject is eligible for the trial.

5.3. IMP Administration

The Subject should be instructed to:

- Take IMP orally once daily for 8 weeks (56 days), preferably around breakfast time, with a glass of water (approximately 240ml);
- When Subjects return for clinic visits or are hospitalized, they will be dosed on site;
- Subjects on the HRZE treatment arm should not take IMP with a meal (generally, no closer to meals than 1 hour before or 2 hours after a meal) and should take the Vitamin B6 25mg supplement with the HRZE dose;
- Subjects on the bedaquiline containing arms should take IMP with a meal (generally allow the Subjects a window of 30 minutes before to 30 minutes after a meal);
- When Subjects return for clinic visits or are hospitalized, they will be dosed on site;

- **For the $J_{(loading\ dose/t.i.w.)}$ DS-TB treatment arm:** The bedaquiline dosing schedule is 400mg daily on days 1-14, and then 200mg 3x per week. The 3x per week doses must be given on the following specific days to accommodate the PK sampling: Days 15, 17, 20, 22, 24, 27, 29, 31, 34, 36, 38, 41, 43, 45, 48, 50, 53 and 56.

5.4. Subject Compliance

During site clinic visits or hospitalization, the IMP will be administered by the Investigator/designated site personnel. During the study, sites will be responsible for ensuring Subjects are taking the IMP correctly and are fully trained on how IMP is to be taken. When possible, Subjects will be checked for IMP compliance by the Investigators or trial personnel/National TB Treatment Program personnel via the hand-and-mouth procedure (both the hand and mouth of the Subject will be checked to ensure that the Subject has swallowed the IMP).

5.5. Blinding and Procedures for Breaking the Blind

This is an open label study. There is no need for blinding or procedures to break the blind.

5.6. IMP Packaging and Labeling

The complete formulations of the bedaquiline, moxifloxacin and PA-824 are found in the applicable Investigator Brochures [12, 13, 23, 36]. The complete formulations of the Pyrazinamide and HRZE combination tablets are found in the applicable Package Insert [11, 37, 40, 42].

5.6.1. Packaging

IMP will be supplied as:

- Bedaquiline 100mg Tablets;
- Moxifloxacin 400mg Tablets;
- PA-824 200mg Tablets;
- Pyrazinamide 500mg Tablets;

- HRZE Tablets (Isoniazid 75mg plus Rifampicin 150mg plus Pyrazinamide 400mg plus Ethambutol 275mg combination tablets).

Subjects will receive the following daily trial medication, depending on which group they are randomized/assigned to (see Table 12 below).

Table 12: Investigational Medicinal Product Details

Treatment Group	Active	Subject Population
$J_{(\text{loading dose/t.i.w.})}PaZ$	Days 1-14 : 4 x bedaquiline 100mg tablets **then** Days 15-56 : 2 x bedaquiline 100mg tablets to be taken 3 times a week on specific study days; Days 15, 17, 20, 22, 24, 27, 29, 31, 34, 36, 38, 41, 43, 45, 48, 50, 53 and 56 **plus** Days 1-56 : 1 x PA-824 200mg tablet **plus** Days 1-56 : 3 x pyrazinamide 500mg tablets	DS-TB
$J_{(200mg)}PaZ$	Days 1-56 : 2 x bedaquiline 100mg tablets **plus** Days 1-56 : 1 x PA-824 200mg tablet **plus** Days 1-56 : 3 x pyrazinamide 500mg tablets	DS-TB
$J_{(200mg)}MPaZ$	Days 1-56 : 2 x bedaquiline 100mg tablets **plus** Days 1-56 : 1 x moxifloxacin 400mg tablet **plus** Days 1-56 : 1 x PA-824 200mg tablet **plus** Days 1-56 : 3 x pyrazinamide 500mg tablets	MDR-TB
HRZE	Days 1-56 : Dosing per weight: 30-37 kg: 2 tablets 38-54 kg: 3 tablets 55-70 kg: 4 tablets 71 kg and over: 5 tablets	DS-TB

5.6.2. Labeling

The test product containing treatment arms will be packaged in an individual treatment pack. The outer packaging of each treatment pack will be labeled with, at a minimum, the following information:

- Name, address and telephone number of the Sponsor
- Name of medication, dosage, quantity and method of administration
- Reference/Lot Number
- Protocol number and space for completion of name of Investigator, site number, treatment number and visit number
- Directions for use
- The statement “For Clinical Trial Use Only”
- Storage conditions
- Expiry date
- The statement “Keep out of reach of children”

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

- Name, address and telephone number of the Sponsor
- Name of medication, dosage, quantity and method of administration
- Reference/Lot Number

- Protocol number and space for completion of name of Investigator, site number, treatment number and visit number
- Directions for use
- The statement “For Clinical Trial Use Only”
- Storage conditions
- Expiry date
- The statement “Keep out of reach of children”

The control product will be commercially purchased and labeled as per the randomization code and the above requirements.

5.7. Storage

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

Test product containing treatment arms will be stored in the supplied containers (thereby protected from light and moisture), between 15 to 30 degrees Celsius.

Control product will be stored per the manufacturers Package Insert, i.e. not exceeding 25 degrees Celsius in the tightly closed container that it 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 trial medication. The Sponsor will take whatever action is required should such a situation arise.

The Investigator undertakes to use the trial medication 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 vendor) who will arrange for destruction after final accountability has been confirmed. If no supplies remain, this fact will be indicated in the drug accountability section of the final report.

6. TRIAL VARIABLES AND PROCEDURES

6.1. Demographic and Baseline Variables and Procedures

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

- Written Informed Consent (including HIV and PK sub-study).
- Eligibility criteria.
- Demographic data: Date of birth, race and gender.
- Medical and treatment history.
- Laboratory parameters: The Safety and Mycobacteriology Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual/s, which will be provided prior to the trial start. The following analyses will be performed:
    - Screening Coached Spot Sputum Sample:
        - Direct microscopy for acid-fast bacilli.
        - Molecular assay for identification of M. Tb and drug susceptibility (such as GeneXpert or MTBDR*plus*) to confirm the diagnosis of TB and distinguish between DS-TB and MDR-TB.
        - Molecular test for fluoroquinolone resistance (such as MTBDR*sl*) for MDR-TB Subjects to establish susceptibility to moxifloxacin.
        - Estimation of adequate sputum production.
    - Overnight Sputum Sample (Days -1 and -2 only):
        - Direct microscopy for acid-fast bacilli.
        - Molecular / antigen test to confirm *M. Tb*.
        - Speciation of infecting organism.
        - Culture: MGIT and Solid Media (quantitative for CFU).
        - DST of *M. Tb* isolate: SIRE, Z.
        - MIC of J, Pa, M.
    - Urine:
        - Urine drug screen.
        - Urine pregnancy test: women of child-bearing potential only, whether they are sexually active or not.
    - Serology:
        - 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 was performed within 1 month prior to trial start, it should not be repeated as long as documentation can be provided (ELISA and/or Western Blot). Prior to HIV testing and on receipt of the results, Subjects will be counseled on HIV by trained counselors if they have indicated as such on the HIV consent form (if approved by the relevant Ethics Committees). If requested by the Subject, HIV counseling provided to the Subject by the study site should be clearly documented in the Subject's medical records/source.

          In the countries and at the sites where 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. For the purpose of this study each individual site has to adhere to its site specific SOPs; country and/or applicable Ethics Committee's specific requirements regarding HIV counseling and HIV result communication.
- Karnofsky Score.
- Tuberculosis Symptom Profile (TSP) Questionnaire.
- Chest X-ray: A chest x-ray picture will be obtained from the clinic appointed radiology department. The Investigator is responsible for review and analysis.

- Concomitant Medications/Other Treatments.
- Height (meters (m)).
- Method of Birth Control: Male and Female Subjects and their partners.
- Verify Post-Trial Treatment TB Programme Attendance: attendance at the local TB clinic, inclusion onto the National TB Treatment Program.

6.2. Efficacy Variables and Procedures

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 efficacy variables will be collected at the time points, and as described, in the trial flow chart:

- Overnight Sputum Sample:
    - TTP (liquid media);
    - Number of CFU per ml sputum (solid media);
    - MIC of J, Pa, M;
    - Direct microscopy for acid-fast bacilli positive/negative and Day;
    - DST of the *M. Tb* isolate: SIRE, Z;
    - Speciation of infecting organism.

- Coached Spot Sputum Sample Collection:
    - TTP (liquid media);
    - Number of CFU per ml sputum (solid media).

Using these observed variables the following derived variables will be assessed for evaluation of the efficacy endpoints:

- The rate of change over timeframes in TTP in liquid and solid media (change in TTP per day);
- The rate of change over timeframes in number of sputum CFU of *M. Tb* on solid media (change in logCFU per day);
- Time to Sputum Culture Conversion;
- Number of Subjects with Sputum Culture Conversion.

6.3. Safety and Tolerability Variables and Procedures

The following safety and tolerability variables will be collected at the time points described in the trial flow chart and assessed for evaluation of the safety endpoints:

- Laboratory parameters. The Safety Laboratory sampling methodology and requirements will be described in a separate document, the Laboratory Manual, which will be provided prior to the trial start. The following analyses will be performed:
    - Hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count);
    - Clinical Chemistry (albumin, BUN, creatinine, direct, indirect and total bilirubin, uric acid, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactic dehydrogenase (LDH), total amylase, lipase, phosphate, sodium, potassium, calcium (corrected for albumin), chloride, magnesium, random/fasting glucose, bicarbonate/CO_2, creatine phosphokinase (CPK) and CK-MB).
    - Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes). Microscopy will be completed as follow up to abnormal urinalysis per discretion of Investigator.
    - Serum Endocrinology: follicle-stimulating hormone (FSH) male Subjects only.
- 12-lead Electrocardiogram (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;
    - ECGs should be recorded prior to other assessments and administration of IMP;
    - 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;
    - Screening ECG to be performed in single, and all other ECGs to be performed in triplicate.
- Vital signs: Supine systolic and diastolic blood pressure (SBP and DBP), heart rate, respiratory rate (RR), body temperature, weight. Using the observed variables weight and height, calculated body mass index (BMI) will be derived.
- Physical Examination:
  - Height is measured at Screening only.
  - Full and Limited (pulmonary, cardiovascular and abdominal) examinations.
- Ophthalmology Examination. The ophthalmology methodology and requirements will be described in a separate document, the Ophthalmology Guideline, which will be provided prior to the trial start. The following analyses will be performed:
  - Ophthalmology History;
  - Visual Acuity Test – Corrected. Near and Distance Vision;
  - AREDS2 opacity typing and grading.
- Adverse Events
  - All AEs and SAEs – through to the end of Day 70 Visit;
  - Only ophthalmologic related adverse events and all serious adverse events - from Day 70 Visit through to Day 140 Visit.
  - Deaths will be reported during the Survival Follow Up Period.
- Concomitant Medication/Other Treatments.
  - Collected up to Day 70 visit.

6.4. Pharmacokinetic Variables and Procedures

Pharmacokinetics:

Pharmacokinetics will consist of two separate schedules:

- *All Subjects:*

  Pre-dose sampling at Days 1, 4, 8, 15, 22, 29, 36, 43, 50 and during the site visit on Days 57 and 70 to measure C_{trough} levels of J, J metabolite M2, M, Pa and Z as per the table 13 below.

- *PK Sub-study Subjects:*

  In addition to the general PK samples, there will be intense PK sampling on Days 14 and 56 at pre-dose, 1, 2, 4, 8 and 24 hours after dosing in a sub-group of 15 Subjects in each treatment arm across selected sites.

Pharmacokinetic Analysis:

All measured PK concentrations will be listed.

For the C_{trough} samples, only descriptive statistics will be prepared (average C_{trough}) derived for each analyte on Days 4, 8, 15, 22, 29, 36, 43, 50, 57 and 70 as follows:

Table 13 : PK Analyte/s per Treatment Arm

Treatment Arm	Analyte/s	Subject Population
$J_{(loading\ dose/t.i.w.)}PaZ$	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}PaZ$	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}MPaZ$	J, J metabolite M2, M, Pa, Z	MDR-TB
HRZE	Z	DS-TB

For the PK sub-study samples, the following PK parameters will be estimated from the individual (per Subject) PK plasma concentrations: minimum observed PK plasma concentration (C_{min}), maximum observed PK plasma concentration(C_{max}), time to reach C_{max} obtained without interpolation (T_{max}), area under the PK plasma concentration time (t) curve from zero to the last quantifiable PK plasma concentration prior to the subsequent dose, using the linear trapezoidal rule ($AUC_{(0-t)}$), area under the PK plasma concentration time (t) curve from zero to 24 hours ($AUC_{(0-24)}$). These will be derived for each analyte, on Days 14 and 56, as follows:

Table 14 : PK Analyte/s per Treatment Arm

Treatment Arm	Analyte/s	Subject Population
$J_{(loading\ dose/t.i.w.)}PaZ$	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}PaZ$	J, J metabolite M2, Pa, Z	DS-TB
$J_{(200mg)}MPaZ$	J, J metabolite M2, M, Pa, Z	MDR-TB
HRZE	Z	DS-TB

$J_{(200mg)}PaZ$ compared to $J_{(loading\ dose/t.i.w.)}PaZ$ and $J_{(200mg)}MPaZ$:

In order to compare the effects of the two J dosing schemes on bedaquiline exposure, the C_{max}, C_{min} and AUC of J and M2 will be compared using PK sub-study data from days 14 and 56 from the $J_{(loading\ dose/t.i.w.)}PaZ$ and $J_{(200mg)}PaZ$ DS-TB arms. A secondary comparison of the PK parameters from the sub-study parameters of J and M2 between the $J_{(200mg)}PaZ$ DS-TB and $J_{(200mg)}MPaZ$ MDR-TB arms will also be performed.

Another comparison of J and M2 exposure will be performed using the C_{trough} data from the $J_{(loading\ dose/t.i.w.)}PaZ$ and $J_{(200mg)}PaZ$ DS-TB arms, with a secondary comparison between the $J_{(200mg)}PaZ$ DS-TB and $J_{(200mg)}MPaZ$ MDR-TB treatment arms.

Pharmacokinetics-Pharmacodynamics (PK-PD):

Pearson correlation coefficients will be reported for the correlation analysis of all relevant PK-PD and exploratory PK-PD endpoints.

Descriptive summary statistics for TMIC will be presented.

6.5. Mycobacteriology Characterization Variables and Procedures

The Mycobacteriology characteristics of the Subjects' *M. Tb* strains will be assessed at the time points described in the trial flow chart.

Overnight Sputum and Coached Spot Sputum Samples will be collected at all scheduled visits, except the Screening Visit when only a Coached Spot Sputum Sample will be collected. Sputum samples will not be collected at Early Withdrawal Visits. Cultures will be grown from all Overnight Sputum and Coached Spot Sputum Samples collected after Day -2. The Overnight Sputum Samples will be considered the reference samples. The following mycobacteriology assays will be carried out:

Table 15 : General Mycobacteriology

Sample	Type	Assessments	Comments
Screening	Coached Spot Sputum Sample	• Direct microscopy for acid-fast bacilli • Molecular assay for identification of *M. Tb* and drug susceptibility (such as GeneXpert or MTBDR*plus*) to confirm the diagnosis of TB and distinguish between DS-TB and MDR-TB • Molecular test for fluoroquinolone resistance (such as MTBDR*sl*) for MDR-TB Subjects to establish susceptibility to moxifloxacin	All to be performed at the Trial Appointed Laboratory.
Baseline Overnight Sputum Samples named Day -2 and -1	Overnight Sputum Sample	• Direct microscopy for acid-fast bacilli • Molecular / antigen test to confirm *M. Tb* • Culture: MGIT and Solid Media (quantitative for CFU) • DST: SIRE, Z • MIC : J, Pa, M • DNA for pncA Sequencing	Z DST resistance must be repeated to confirm.
Baseline Coached Spot Sputum Sample named Day -2 and -1	Coached Spot Sputum Sample	• Culture: MGIT and Solid Media (quantitative for CFU)	For determination of logCFU and logTTP rates of change for comparison to cultures from Overnight Sputum Sample.
Overnight Sputum Sample named Days 1, 3, 7, 14, 21, 28, 35, 42, 49 and 56	Overnight Sputum Sample	• Culture: MGIT and Solid Media (quantitative for CFU) • The last positive sample from withdrawn Subjects who have not converted to culture negative status OR Subjects who are still culture positive at 8 weeks OR the first positive sample after conversion to culture negative status for Subjects who have 'relapsed'*****: o DST : SIRE, Z o MIC : J, Pa, M	
Coached Spot Sputum Sample Days 1, 3, 7, 14, 21, 28, 35, 42, 49 and 56	Coached Spot Sputum Sample	• Culture: MGIT and Solid Media (quantitative for CFU)	For determination of logCFU and logTTP rates of change for comparison to cultures from Overnight Sputum Sample.

- The above assays will be carried out according to procedures described in the Laboratory Manual.

- The Coached Spot Sputum Sample can be used for all assays, except CFU and TTP, if results cannot be obtained from the Overnight Sputum Sample.
- pncA sequencing and MIC isolates can be batched at the end of the study.
- *****If the Subject was treated with study medication for less than 9 days, the mycobacteriology testing will be performed on the Day -2 sample isolate only.
- *****Culture negativity is defined as the first two consecutive negative cultures, except for the week 8 time point, where a singular negative is acceptable.

7. ADVERSE EVENTS

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

Adverse events will be collected by the Investigator from the time a Subject signs the Informed Consent Form until the Subject has completed their last follow-up as follows:

- All AEs and SAEs – through to the end of the Day 70 Visit;
- Only ophthalmologic related AEs and all SAEs - from Day 70 through to Day 140 Visit
- Deaths will be reported during the Survival Follow Up period.

7.1. Definitions

7.1.1. Adverse Event (AE)

Any untoward medical occurrence in a patient 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

The definitions for rating attribution/causality will be as described in Table 16.

Table 16: Adverse Events Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An adverse event, which is not related to the use of the drug.
Unlikely	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.
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).
Certain	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 2). For abnormalities **NOT found** elsewhere in the Toxicity Tables the scale described in Table 17 below is to be used to estimate grade of severity:

Table 17: Adverse Event Severity Ratings

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	Severity Rating	Definition
GRADE 4	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
- Hospitalization or prolongation of hospitalization
- 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 as follows:

- All AEs and SAEs will be collected through to the end of the Day 70 Visit;
- Only ophthalmologic related AEs and all SAEs from the Day 70 Visit through to the end of the Day 140 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 study 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.

Serious Adverse events will be collected by the Investigator from the time a Subject signs the Informed Consent Form as follows:

- All AEs and SAEs will be collected through to the end of the Day 70 Visit;
- Only ophthalmologic related AEs and all SAEs from the Day 70 Visit through to the end of the Day 140 Visit;
- Deaths will be reported during the Survival Follow Up period.

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 study drug and the seriousness of the AE in question to the study monitor and medical monitor within 24 hours of becoming aware of the SAE.

The study 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 study monitor and medical monitor with a newly completed Serious Adverse Event Form, designated as a follow-up report. This will be submitted to the study monitor and medical monitor within 24 hours of the Investigator receiving the information.

The study 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 Sponsor.

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 certainly 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 (Pulmonary Tuberculosis) experienced by the Subject while on the study will be assessed by the Investigator. If the symptom has:

- worsened while the Subject is in the study; 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 study, 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 the trial;
- Within 6 months after last dose of IMP.

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 study or in the 6 months 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 ongoing 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. Grade 3 and grade 4 laboratory abnormalities and laboratory abnormalities considered clinically significant should be followed until satisfactory resolution or stabilization.

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 is based upon target organs defined in preclinical toxicity studies (Investigator's Brochures [12, 13, 23, 36] and Package Inserts [11, 37, 40, 42]).

7.3.1. ALT and AST

> 1.0 to < 5.0 x ULN AST or ALT elevation:

Management will be at the discretion of the Investigator, according to generally accepted medical practice standards, and Subjects may continue IMP. Subjects should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.

≥ 5.0 x ULN or Grade 4 (> 8.0 x ULN) AST or ALT elevation:

Subjects will permanently discontinue IMP and be withdrawn from the trial. It is recommended that the Investigator contacts the Sponsor to discuss the case of AST or ALT elevation. Subjects should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.

7.3.2. Amylase elevation

Grade 1 (> 1.0 to ≤ 1.5 x ULN) or Grade 2 (> 1.5 to ≤ 2.0 x ULN):

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

Grade 3 (> 2.0 to ≤ 5.0 x ULN):

Further testing such as pancreatic amylase and trypsin-like immunoreactivity should be considered after consultation with the Sponsor Medical Monitor.

Grade 4 (≥ 5.1 x ULN):

Subjects with **confirmed Grade 4** elevations of total amylase will permanently discontinue study medication and be withdrawn from the trial.

7.3.3. Lipase elevation

Grade 1 (> 1.0 to ≤ 1.5 x ULN) or Grade 2 (> 1.5 to ≤ 2.0 x ULN):

Management will be at the discretion of the Investigator, according to generally accepted medical practice standards. Subjects may continue IMP and should be carefully evaluated and followed closely.

Grade 3 (> 2.0 to ≤ 5.0 x ULN) or Grade 4 (≥ 5.1 x ULN):

Subjects with **confirmed Grade 3 or 4** elevations of lipase will permanently discontinue IMP and be withdrawn from the trial.

7.3.4. Musculo-skeletal System and Cardiac Muscle

Myalgia

Grade 1 (mild with no limitation of activity):

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

Grade 2 (muscle tenderness at site other than injection site or with moderate impairment of activity) or Grade 3 (severe muscle tenderness with marked impairment of activity) or Grade 4 (frank myonecrosis):

Subjects will permanently discontinue IMP and be withdrawn from the trial. CPK should be fractionated for CK-MB subunit.

Subjects having **Grade 3 (3.1 to 6 x ULN) or Grade 4 (> 6 x ULN) elevation in CK-MB subunit** will permanently discontinue IMP and be withdrawn from the trial.

7.3.5. LDH

For Subjects with LDH elevation >2.5 x ULN, LDH isoenzymes will be assessed.

7.3.6. Cardiac Rhythm Disturbances

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:

Subjects will permanently discontinue IMP and be withdrawn from the trial.

QTc prolongation

A Subject will be withdrawn if:

- the mean QTcF of their triplicate recordings is equal to or greater than 500 msec, or
- if a single recording has a QTcF ≥ 500msec, the ECG should be repeated. If the second ECG also has a QTcF of ≥ 500msec the Subject should be withdrawn after consultation with the Sponsor, or
- they develop a new left bundle branch block (LBBB) or Mobitz type 2 or complete heart block. Recordings with artifacts that interfere with the interpretation of the ECG should be repeated to confirm the findings.

If the finding is from the centralized ECG machine reading the result is to be checked and confirmed by the Investigator. If this is confirmed by the Investigator, dosing is to be withheld until the reading has been confirmed by the central cardiologist and the Subject is to be treated per the Investigators clinical judgment. If it is confirmed by the central cardiologist the Subject is to be withdrawn.

7.3.7. Other toxicities

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 (see Appendix 2 for specifics) 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 study. 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 study team. It will comprise at least 3 voting members. The DSMC may have an organizational meeting prior to commencement of the trial. The DSMC will have one meeting where it will review unblinded data during a closed session. This meeting is planned to occur once 33% of the planned Subjects' complete treatment. 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

The statistical analysis plan (SAP), which will contain details of the analyses described generally in this section, will be written and signed off prior to Clinical Database Lock.

8.1. Analysis Population

Efficacy Analysis Populations will contain all Subjects included in the safety analysis population for whom corresponding efficacy data are available and had no major protocol violations/deviations defined as violations/deviations affecting the integrity of the efficacy data.

The analysis populations will be defined in the SAP.

In particular, the Safety analysis population will contain all Subjects who were randomized to study drug and received at least one administration of study drug. The Efficacy analysis populations will contain all Subjects included in the Safety analysis population for whom corresponding efficacy data are available and had no major protocol violations/deviations defined as violations/deviations affecting the integrity of the efficacy data. Pyrazinamide resistant subjects will be excluded from the general efficacy analyses, except for the exploratory analyses associated with the comparison of MDR-TB pyrazinamide resistant subjects to MDR-TB sensitive subjects.

8.2. Sample Size

The objective of this trial is to evaluate the bactericidal activity, safety, tolerability and pharmacokinetics of combinations of bedaquiline, PA-824, moxifloxacin and pyrazinamide after 8 weeks of treatment.

Sixty subjects will be randomized to each DS treatment group. It is expected that at least 50 subjects per treatment group would have valid data for the assessment of $BA_{TTP}(0\text{-}56)$ as per primary efficacy analysis.

A fixed number of MDR subjects to be assigned is not pre-specified. The analysis of such MDR subjects is exploratory and no formal statistical analysis will therefore be performed for the MDR treatment group.

Formal sample size calculations will not be performed due to the exploratory nature of the trial (no formal statistical hypothesis is therefore to be tested). Provided the assumption that a sample size of 50 subjects in each DS treatment group will be included, and using a two sample t-test with a 0.05 two-sided significance level (alpha) with common standard deviation (SD) of 0.008, the study will have 90% statistical power to detect a mean group difference in BA_{TTP}(0-56) of 0.00524.

8.3. Interim Analyses

No formal interim analyses will be done for this study. The survival follow-up analysis will be included as an Addendum to the final CSR.

8.4. Primary Endpoint Analysis

The primary efficacy analysis of the primary efficacy endpoint, i.e. BA_{TTP}(0-56), as determined by the rate of change in the log TTP in sputum over 8 weeks of treatment, will be analyzed using non-linear mixed effects (NLME) regression modeling.

Sensitivity analyses may be performed using different model assumptions for the NLME regression model.

Subgroup analyses, such as by site and human immunodeficiency virus (HIV) status, may be performed as exploratory analyses.

No multiplicity adjustments for alpha will be done as this is an exploratory trial.

8.5. Secondary Endpoint Analysis

8.5.1. Efficacy

The secondary efficacy endpoints and analyses are as follows:

- The BA_{CFU}(0-56), BA_{CFU}(0-2) and BA_{CFU}(14-56) as determined by the rate of change in log colony forming units (CFUs) over Days 0 to 2 and Days 14 to 56 treatment, represented by the model-fitted log(CFU) counts as calculated by the regression of the observed log(CFU) counts over time.
- The BA_{TTP}(0-2) and BA_{TTP}(14-56) as determined by the rate of change in log time of sputum culture positivity (TTP) over 8 weeks of treatment in the Mycobacterial Growth Indicator Tube system, represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time.
- Time to sputum culture conversion using data from weekly cultures through 8 weeks of treatment (separately, on solid and liquid media).
    - The time to sputum culture conversion will be analyzed using Kaplan-Meier analysis, and will be depicted in figures. Time to sputum culture conversion is defined as the sampling day at which first of two consecutive negative cultures are obtained (except for the week 8 time point where a singular negative sample is sufficient). The log-rank test will be used for the comparison of the median time to sputum culture conversion.
- Proportion of subjects with sputum culture conversion at 4, 6 and 8 weeks (separately, on solid and liquid media).
    - The proportion of Subjects with sputum culture conversion at each time point will be compared pairwise between treatment groups using a Chi-Square test.
- The BA_{CFU}(0-56, 0-2 and 14-56) and BA_{TTP}(0-56, 0-2 and 14-56) of $J_{(\text{loading dose/t.i.w.})}$PaZ compared to $J_{(200mg)}$PaZ from DS-TB treatment arms.
- Investigation of the methodology of sputum sampling by comparing CFU counts and TTP results, quantified by both coached spot and overnight sputum samples.
- All analyses of the CFU an TTP data obtained by overnight sputum sampling will also be performed for CFU and TTP data obtained on the coached spot sputum samples.

8.5.2. Safety and Tolerability Analysis

- 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).
- Treatment-emergent adverse events (TEAEs) are defined as AEs which started at or after the first administration of IMP and includes those events started prior to the first administration of IMP but which worsened after the first intake. Adverse events starting after the last administration of IMP until the last scheduled visit/assessment/measurement will be regarded as treatment-emergent.
- The incidence of the following events will be summarized by treatment group for further medical analysis:
    - Incidence of 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.
- Cardiovascular Safety (see Appendix 3). ECGs will be centrally read. 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.
    - Tukey honestly significant difference (HSD) analysis of the mean change from baseline in QTcB and QTcF interval between treatment groups across all post-baseline values.
- Ophthalmology: Descriptive statistics will be presented for ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2] lens opacity classification and grading) and listed by Subject. Categorical data for lens opacity will be summarized in a frequency table for the left and right eye, respectively.
- Other safety variables: Laboratory Parameters, Physical Examination, Vital signs (see Appendix 3), Concomitant medication. Descriptive summary statistics will be presented. The incidence of liver related laboratory abnormalities will be explored.
- Survival Follow Up status per contact will be summarized descriptively. This analysis will be included as an Addendum to the final CSR.

8.5.3. Pharmacokinetics:

For each analyte (per visit), the PK plasma concentrations and parameters will be summarized by descriptive statistics, including the mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and geometric CV (%).

In addition, mean and median concentration-versus-time graphs will be provided (with error bars as appropriate).

8.5.4. Pharmacokinetics-Pharmacodynamics (PK-PD):

- Pearson correlation coefficients will be reported for the correlation analysis of all relevant PK-PD and exploratory PK-PD endpoints.
- Descriptive summary statistics for TMIC will be presented.

8.6. Exploratory Endpoint Analysis

8.6.1. Efficacy

The exploratory efficacy endpoints and analyses are as follows:

- Sub-analysis of the primary and secondary efficacy endpoints of the MDR-TB pyrazinamide resistant subjects compared to the MDR-TB sensitive subjects.
- Sub-analysis of the primary and secondary efficacy endpoints of the H or R mono-resistant subjects will be evaluated as separate sub-groups.

8.7. General Mycobacteriology

Descriptive summary statistics for the mycobacterial characteristics 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/eCRF will be completed. For Subjects who are prematurely withdrawn, the visits up to withdrawal plus the withdrawal and applicable 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.

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

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 study. However the Investigator maintains responsibility for the study and will supervise the Sub-Investigators. Written IEC/IRB approval will be obtained prior to involvement in the study.

The Investigator will ensure that all site personnel are adequately trained in GCP, the protocol, IB and all study 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. A risk based monitoring approach will be followed. 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 study. Visits will take place usually within a predetermined interval, but this may vary during the course of the study. The Investigator and site staff will allow the study 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 studies are in accordance with the guidelines. Having the highest quality data from studies 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 study. The audit will involve the review of all study-related documentation required by GCP to be maintained by each site; drug storage, dispensing and return; all study-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 these required study related documents will be reviewed by the sites' respective IEC/IRB. The study will not start 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. 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 study, in accordance with International GCP, applicable local legislation/regulations. Subject to the requirement for source data verification by the study personnel by reference to the Subject's notes, confidentiality of all Subject identities will be maintained. Only Subject study number and initials will be used on the CRF and in all study 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 study.

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 study 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 study Sponsor and funder 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 Subjects will not receive any incentives for their involvement in the study. The Sponsor has made provision to reimburse the Subjects for out-of-pocket expenses such as travelling to and from the study site and other miscellaneous costs as a result of their study 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.

15. REFERENCES

1. Maggi N, Pasqualucci CR, Ballotta R, Sensai P. Rifampicin: A new orally active rifamycins. Chemotherapy 1966; 11 (5): 285-92.
2. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 1980; 121 (6): 939-49.
3. Dietze R, Teixeira L, Rocha LMC, et al. Safety and bactericidal activity of rifalazil in patients with pulmonary tuberculosis. Antimicrob Agents Chemother 2001; 47 (7): 1972-6.
4. Donald PR, Sirgel FA, Venter A, et al. Early bactericidal activity of antituberculosis agents. Expert Rev Anti-infect Ther 2003; 1 (1): 141-55.
5. Johnson JL, Hadad DJ, Boom WH, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2006; 10 (6): 1-8.
6. Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Chemother 2008 Aug; 52(8): 2831-5. Epub 2008 May 27.
7. Donald PR, Diacon AH. The early bactericidal activity of anti-tuberculosis drugs: a literature review. Tuberculosis 2008; 88 Suppl 1: S75-S83.
8. Brindle RJ, Nunn PP, Githui W, Allen BW, Gathua S and Waiyake P. Quantitative bacillary response to treatment in HIV-associated pulmonary tuberculosis. Am Rev Respir Dis 1993; 147:958-961.
9. Rustomjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, Reddy C, Sturm AW, Sirgel FA, Allen J, Coleman DJ, Fourie B, Mitchison DA; Gatifloxacin for TB (OFLOTUB) study team. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2008 Feb; 12(2):128-38.
10. Davies GR, Brindle R, Khoo SH and Aarons A. Use of Nonlinear Mixed-Effects Analysis for Improved Precision of Early Pharmacodynamic Measures in Tuberculosis Treatment.] LJ. Antimicrob Agents Chemother. 2006 September; 50(9): 3154–3156.
11. Package Insert, Sirturo™, Janssen Therapeutics, February 2012.
12. TMC207 Investigator's Brochure, Janssen Research and Development, Edition 7, 18 September 2012.
13. TMC207 Addendum 1 to Investigator's Brochure Edition 7, 3 July 2013.
14. Koul A, Dendouga N, Vergauwen K, et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. Nat Chem Biol 2007; 3: 323-4.
15. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium turberculosis. Science 2005; 307: 223-7.
16. Huitric E, Verhasselt P, Andries K, Hoffner SE. In vitro antimycobacterial spectrum of a diarylquinoline ATP synthase inhibitor. Antimicrob Agents Chemother 2007; 51: 4202-4.
17. Koul A, Vranckx L, Dendouga N, et al. Diarylquinolines are bactericidal for dormant mycobacteria as a result of disturbed homeostasis. J Biol Chem 2008; 283: 25273-80.
18. Mdluli K, Nuermberger, E. Pre-Clinical Drug Combination Studies to Identify Novel Regimens for TB. In: Recent Advances in TB Drug Development symposium, 40th Union World Conference, International Union Against TB and Lung Disease, Cancun, Mexico, 2009.
19. Mdluli K , Nuermberger E, Taylor K, Williams N, Koen A, Khisimuzi E, Rokeya T, Si-Yang L, Peloquin C, Dinesh C, Sterilizing activity of novel TMC207- and PA-824-containing regimens in a murine model of tuberculosis. Antimicrobial Agents and Chemotherapy 2011; 55: 5485-5492.

20. Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Chemother 2008 Aug; 52(8): 2831-5. Epub 2008 May 27.
21. Diacon AH, Dawson R, Von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, Conradie A, Erondu N, Ginsberg AM, Egizi E, Winter H, Becker P, Mendel CM, Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum microscopy smear-positive pulmonary tuberculosis. Antimicrob Agents Chemother. 2013 May;57(5):2199-203. doi: 10.1128/AAC.02243-12. Epub 2013 Mar.
22. Diacon AH, Dawson R, von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, van Niekerk C, Everitt D, Winter H, Becker P, Mendel CM, Spigelman MK. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. Lancet. 2012 Sep 15;380(9846):986-93. doi: 10.1016/S0140-6736(12)61080-0. Epub 2012 Jul 23.
23. Investigator's Brochure, Global Alliance for TB Drug Development, PA-824, Version 15, 31 January 2013.
24. Stover, C. K., P. Warrener, D. R. VanDevanter, et al. 2000. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature 405:962–966.
25. Anne J. Lenaerts, Veronica Gruppo, Karen S. Marietta, Christine M. Johnson, Diane K. Driscoll, Nicholas M. Tompkins, Jerry D. Rose, Robert C. Reynolds, and Ian M. Orme. Preclinical Testing of the Nitroimidazopyran PA-824 for Activity against Mycobacterium tuberculosis in a Series of In Vitro and In Vivo Models. Antimicrob Agents Chemother. 2005 June; 49(6): 2294–2301.
26. Baohong PI, Lounis N, Maslo C, Truffot-Pernot C, Bonnafous P, Grosset J. In vitro and in vivo activities of moxifloxacin and clinafloxacin against Mycobacterium tuberculosis. Antimicrob.Agents Chemother. 1998; 42(8):2066-9.
27. Miyazaki E, Miyazaki M, Chen JM, Chaisson RE, Bishai WR. Moxifloxacin (BAY12-8039), a new 8-methoxyquinolone, is active in a mouse model of tuberculosis. Antimicrob. Agents Chemother. 1999; 43(1):85-9.
28. Nuermberger EL, Yoshimatsu T, Tyagi S, O'Brien RJ, Vernon AN, Chaisson RE et al. Moxifloxacin-containing regimen greatly reduces time to culture conversion in murine tuberculosis. Am.J.Respir.Crit.Care Med. 2003; 169:421-6.
29. O'Brien RJ. Scientific blueprint for tuberculosis drug development. Tuberculosis 2001; 81(S1):19-45.
30. Gosling RD, Uiso LO, Sam NE, Bongard E, Kanduma EG, Nyindo M et al. The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis. Am J Respir Crit Care Med 2003; 168 (11):1342-5.
31. Pletz MWR, De Roux A, Roth A et al. Early Bactericidal Activity of Moxifloxacin in Treatment of Pulmonary Tuberculosis: a Prospective, Randomized Study. Antimicrob. Agents Chemother 2004; 48 (3); 780-2.
32. Burman W, Goldberg S, Johnson JL, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. Am J Respir Crit Care Med 2006; 174: 331-38.
33. Rustomjee R, Lienhardt C, Kanyok T et al. Gatifloxacin for TB (OFLOTUB) study team. A phase II study of the sterilizing activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2008; 12:128-38.
34. Conde MB, Efron A, Loredo C et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomized, controlled phase II trial. Lancet 2009; 373: 1183-89.

35. Dorman SE, Johnson JL, Goldberg S, et al. Substitution of Moxifloxacin for Isoniazid during Intensive Phase Treatment of Pulmonary Tuberculosis. Am J Respir Crit Care Med 2009; 180: 273-80.
36. Investigator's Brochure, Bayer HealthCare AG, moxifloxacin, Version 14, 01 Oct2011.
37. Package Insert, Moxifloxacin, Macleods Pharmaceuticals Ltd, 01/2014, Version 0.1.
38. Zhang Y and Mitchison D. The curious characteristics of pyrazinamide: a review. Int J Tuberc Lung Dis; 7 (1): 6-21.
39. Rokeya Tasneen, Sandeep Tyagi, Kathy Williams, Jacques Grosset, and Eric Nuermberger Enhanced Bactericidal Activity of Rifampin and/or Pyrazinamide When Combined with PA-824 in a Murine Model of Tuberculosis. Antimicrob Agents Chemother 2008 Oct; 52(10): 3664–8.
40. Package Insert, Rifampicin/Isoniazid/Pyrazinamide/Ethambutol, Macleods Pharmaceuticals Ltd., September 2011.
41. Botha FJH, Sirgel FA, Parkin DP, van de Wall BW, Donald PR, Mitchison DA. Early bactericidal activity of ethambutol, pyrazinamide and the fixed combination of isoniazid, rifampicin and pyrazinamide (RIFATER) in patients with pulmonary tuberculosis. South African Medical J 1996; 86: 155-158.
42. Package Insert, Pyrazinamide, Macleods Pharmaceuticals Ltd, November 2012.
43. GlaxoSmithKline. Study Report. Technical Report no. 2011N119717_01. Model-based assessment of the feasibility of a 1500 mg fixed dose regimen of pyrazinamide and its impact on systemic drug exposure and liver safety in patients with tuberculosis. 2011.
44. Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109.

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	exact figure/100/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 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 patients 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
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	$\geq$ 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	$\geq$ 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 3 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**	**RR**
Abnormalities on actual values				
"Abnormally low"	≤ 50 bpm	≤ 50 mmHg	≤ 90 mm Hg	<12 Breaths per minute
"Grade 1 or mild"	-	> 90 mmHg-<100 mmHg	> 140 mmHg-<160 mmHg	17-20 Breaths per minute
"Grade 2 or moderate"	-	≥ 100 mmHg-<110 mmHg	≥ 160 mmHg-<180 mmHg	21-25 Breaths per minute
"Grade 3 or severe"	-	≥ 110 mmHg	≥ 180 mmHg	>25 Breaths per minute
"Abnormally high or Grade 4"	≥ 120 bpm	-	-	Intubation

APPENDIX 4 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 5 TUBERCULOSIS SYMPTOM PROFILE (Version 3)

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

Please read each symptom carefully to the patient and provide them time to think about their experience during the past 7 days before you mark their response below. Tick (☑) only one box for each symptom.

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

If they did experience the symptom during the last 7 days, please tick (☑) whether the intensity of the symptom they experienced was "mild", "moderate", or "severe".

TB Symptom	**Rate the patient's experience of each symptom during 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 the patient rate the quality of their appetite? **□ Good □ Fair □ Poor**				

Approved, Issued date: 09-Apr-2012: adopted by Global Alliance for TB Drug Development

Completed by: _____ Date completed: _____