CONFIDENTIAL

Protocol Title:

A Phase 2 Trial to Evaluate the Early Bactericidal Activity, Safety and Tolerability of Meropenem Administered Intravenously Once or Twice Daily in Combination with Oral Amoxicillin/Clavulanate, Ertapenem Administered Once Daily Intravenously or Intramuscularly with Oral Amoxicillin/Clavulanate, Oral Amoxicillin/Clavulanate Alone, and Rifampicin with Oral Amoxicillin/Clavulanate in Adults with Newly Diagnosed, Smear-Positive Rifampicin-Susceptible Pulmonary Tuberculosis

Protocol Number: TASK-003

Protocol Version: Version 1.2

Protocol Date: 27 February 2020

Sponsor Protocol Signature Page

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Protocol Number: TASK-003

Protocol Date: 27 February 2020

Sponsor

I agree to the terms of this study protocol.

_____ _____

Signature of Sponsor/Sponsor Representative Printed Name

_____

Date

Principal Investigator Protocol Signature Page

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Protocol Number: TASK-003

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Principal Investigator

I agree to the terms of this study protocol.

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Signature of Principal Investigator Printed Name

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Date

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List of Abbreviations and Definitions of Terms

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AMX	Amoxicillin
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
BD	Twice Daily
CA	Clavulanic Acid
CFU	Colony Forming Units
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum Observed Plasma Concentration at the End of the Dosing Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DR	Drug Resistant
DS	Drug Sensitive
EBA	Early Bactericidal Activity
EC	Ethics Committee
ECG	Electrocardiogram
EMB	Ethambutol
EWV	Early Withdrawal Visit
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid/Rifampicin/Pyrazinamide/Ethambutol
IB	Investigator Brochure
ICF	Informed Consent Form
IF	Incidental Findings
IV	Intravenous
IP	Investigational Product
IUATLD	International Union Against Tuberculosis and Lung Disease
INH	Isoniazid
LDH	Lactate Dehydrogenase
m	Meters
MDR	Multi Drug Resistant
MGIT	Mycobacterial Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
MOXI	Moxifloxacin
MTB	*Mycobacterium Tuberculosis*
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PI	Principal Investigator

PK	Pharmacokinetic
PR	Electrocardiographic PR Interval
PZA	Pyrazinamide
QT	Electrocardiographic QT Interval
QTc	Corrected QT Interval
RIF/RF	Rifampicin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
t	Time
t½	Apparent Terminal Elimination Phase Half-Life
TB	Tuberculosis
TEAEs	Treatment-Emergent Adverse Events
T_{max}	Time at Which C_{max} is Observed
TMIC	Time over Minimum Inhibitory Concentrations
TTP	Time to Sputum Culture Positivity
ULN	Upper Limit of Normal
WHO	World Health Organization
XDR	Extensively Drug Resistant

EBA Definitions

EBA	An agent's ability to kill mycobacteria originating within pulmonary cavities during the first weeks of treatment.
EBA $_{CFU}$	Determination of EBA by quantification of solid medium of viable Colony Forming Units (CFU) of *M. Tuberculosis* from an overnight sputum collection.
EBA $_{TTP}$	Determination of EBA by measurement in an automated liquid culture system of time to positivity (TTP) of *M. Tuberculosis* from an overnight sputum collection.

1. Protocol Synopsis

1.1 Synopsis

Name of Sponsor/Company:	TASK Foundation NPC, funded by the European Union (Horizon 2020)
Name of Finished Products:	Meropenem ; Ertapenem; Rifampicin; Amoxicillin/CA
Protocol Title:	A Phase 2 Trial to Evaluate the Early Bactericidal Activity, Safety and Tolerability of Meropenem Administered Intravenously Once or Twice Daily in Combination with Oral Amoxicillin/Clavulanate, Ertapenem Administered Once Daily Intravenously or Intramuscularly with Oral Amoxicillin/Clavulanate, Oral Amoxicillin/Clavulanate Alone, and Rifampicin with Oral Amoxicillin/Clavulanate in Adults with Newly Diagnosed, Smear-Positive Rifampicin-Susceptible Pulmonary Tuberculosis.
Treatment Indication:	Pulmonary tuberculosis (TB).
Trial Objective:	The overall objective of this study is to evaluate the 2-week bactericidal activity and pharmacokinetics of the following beta-lactam containing combinations with the aim to select the most active and implementable solution to be incorporated into a drug-resistant TB combination regimen: • Once or twice daily meropenem administered intravenously in combination with once or twice daily oral amoxicillin/clavulanic acid; • Once daily ertapenem administered intravenously and intramuscularly in combination with twice daily oral amoxicillin/clavulanic acid; • Twice daily oral amoxicillin/clavulanic acid; • Once daily rifampicin administered orally at highest currently established dosage of 35mg/kg in combination with twice daily oral amoxicillin/clavulanic acid.

Name of Sponsor/Company:	TASK Foundation NPC, funded by the European Union (Horizon 2020)
Name of Finished Products:	Meropenem ; Ertapenem; Rifampicin; Amoxicillin/CA
Trial Design:	A single-center, open-labeled, clinical trial in two groups. The treatments are: Group 1: 1. Meropenem 6g intravenously once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 2. Ertapenem 1g intramuscularly once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. Group 2: 3. Meropenem 3g intravenously twice daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 4. Ertapenem 1g intravenously once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 5. Amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 6. Rifampicin 35 mg/kg once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 7. Meropenem 6g OR meropenem 4g intravenously once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally once daily on days 1–14. A total of 4 participants per group will receive standard first line TB treatment as per the South African TB guidelines (Rifafour e-275®) and is included as a control for the EBA quantitative mycobacteriology and to evaluate whether HRZE gives similar EBA results to that demonstrated in prior studies with this combination. The mycobacteriology laboratory will remain blinded until closure of the EBA results. Enrollment into group 1 will be completed before enrollment into group 2 will start. After completion of enrollment into group 1, there will be an interim analysis while enrollment into group 2 is ongoing.
Patient Population:	A total of 113 male or female participants (7 groups of 15 participants receiving IP and 2 groups of 4 participants receiving Rifafour e-275®), aged between 18 and 65 years (inclusive), with newly diagnosed, smear-positive, pulmonary TB.

Name of Sponsor/Company:	TASK Foundation NPC, funded by the European Union (Horizon 2020)
Name of Finished Products:	Meropenem ; Ertapenem; Rifampicin; Amoxicillin/CA
Test Product, Dose and Mode of Administration:	The Investigational Product (IP) will be supplied as: • Meropenem 1g reconstitution vials • Ertapenem 1g reconstitution vials • Amoxicillin/CA 1000/62.5mg tablets • Rifampicin 150mg and 300mg tablets Treatment will be administered for 14 consecutive days in the following dosing schemes: 1. Meropenem 6g intravenously once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 2. Ertapenem 1g intramuscularly once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 3. Meropenem 3g intravenously twice daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 4. Ertapenem 1g intravenously once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 5. Amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 6. Rifampicin 35 mg/kg once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally 12-hourly on days 1-14. 7. Meropenem 6g OR 4g intravenously once daily; plus amoxicillin/CA 2 x 1000mg/62.5mg orally once daily on days 1 – 14.
Positive Control Product, Dose, and Mode of Administration:	Rifafour e-275® will be supplied as tablets and administered orally once daily for 14 days as per South African National TB Treatment Guidelines. The daily dose is dependent on the participants' weight as follows: 40 - 54kg: 3 tablets; 55 – 70kg: 4 tablets; 71kg and over: 5 tablets.

Criteria for evaluation:

Primary Endpoint Analysis

The EBA_{CFU}(0-14) as determined by the rate of change in logCFU per ml sputum over the period day 0 to day 14 which will be described with at most 3 parameters from a linear, bi-linear or non-linear regression of logCFU on time.

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

Secondary Endpoint Analysis

Activity:

- The EBA_{CFU}(0-2) and EBA_{CFU}(2-14) as determined by the rate of change of logCFU in sputum over the period day 0 to day 2 and day 2 to day 14, which will be described with at most 3 parameters from an appropriate function of logCFU on time.
- The EBA_{TTP}(0-2), EBA_{TTP}(0-14), and EBA_{TTP}(2-14) in the Mycobacterial Growth Indicator Tube (Bactec™ MGIT™ 960) system as determined by the rate of change in TTP in sputum over the periods day 0 to day 2, day 0 to day 14, and will be described with at most 3 parameters from an appropriate function of TTP on time.

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

Safety and Tolerability Analyses

- 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 IP and includes those events that started prior to the first administration of IP but which worsened after the first intake. Adverse events starting after the last administration of IP 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 treatment-emergent adverse events (TEAEs);
  - Incidence of TEAEs by Severity;
  - Incidence of drug related TEAEs;
  - Incidence of Serious TEAEs;
  - Incidence of TEAEs leading to early withdrawal;
  - Incidence of TEAEs leading to death.
- Other safety variables: laboratory parameters, physical examination, vital signs, concomitant medication. Descriptive summary statistics will be presented.

Pharmacokinetic Analysis

The maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), the minimum observed plasma concentration (C_{min}) 24 hours following day 14, area under the plasma concentration time (t) curve from zero to 24 hours (AUC(0-24)) will be estimated for the following, on day 14:

Treatment Arm	**Analyte/s**
Meropenem plus amoxicillin/CA	Meropenem; amoxicillin; CA
Ertapenem plus amoxicillin/CA	Ertapenem; amoxicillin; CA
Rifampicin	Rifampicin; amoxicillin; CA
Amoxicillin; CA	Amoxicillin; CA
Rifafour e275®	None

No PK analyses will be performed on the Rifafour e275® treatment arm.

The following PK parameters will be estimated from participants' individual plasma concentrations (except in the Rifafour e275® treatment arm) by applying a noncompartmental approach using PK software such as WinNonlin Professional. Concentration values reported as below the limit of quantitation will be set to zero. Each parameter will be calculated separately using plasma concentrations of meropenem and ertapenem and their respective metabolites, amoxicillin/CA and rifampicin. PK parameters will be estimated for day14 only.

- C_{max}: Maximum observed plasma drug concentration.
- T_{max}: Time at which C_{max} is observed (obtained without interpolation).
- C_{min}: Minimum observed plasma drug concentration 24 hours following the last dose.
- AUC(0-24): Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 24 hours.

Descriptive statistics including mean, standard deviation, coefficient of variation, median, minimum and maximum, geometric mean and geometric mean CV% will be computed for each PK parameter by group. Grouping will be by gender.
In addition, mean and median concentration-versus-time graphs will be provided (with error bars as appropriate).

Pharmacokinetic and Pharmacodynamic Analysis

The EBA_{CFU}(0-14), EBA_{CFU}(0-2), and EBA_{CFU}(2-14) vs. the following PK variables will be presented for Meropenem, ertapenem, amoxicillin/CA, and rifampicin:

- C_{max};
- AUC(0-24);
- Time over minimum inhibitory concentrations (TMIC).

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

No PK-PD analyses will be performed on the Rifafour e275® treatment arm.

Mycobacteriology Characterization

Name of Sponsor/Company:	TASK Foundation NPC, funded by the European Union (Horizon 2020)
Name of Finished Products:	Meropenem ; Ertapenem; Rifampicin; Amoxicillin/CA

Cultures grown from the overnight sputum collections from Baseline (day -2 or day -1) and the last available culture on a treatment day will be assessed as follows:

- A culture will be grown from a sputum sample submitted before treatment initiation (baseline) for confirming that the infecting organism is *M. tuberculosis* susceptible to isoniazid and rifampicin (GenoType MTBDRplus, Hain, Nehren, Germany). Cultures from baseline and from day 14 sputum will be kept for determination of the minimum inhibitory concentration (MIC) of the investigational agents that the subject was treated with. If a Day 14 culture is not available the last available culture after Day 8 will be kept. MIC tests for beta-lactams are under development and cultures might be exported for this purpose.

Statistical Methods:

This is a descriptive study with no inferential statistics or hypothesis testing. The planned sample size of 15 participants per treatment group is in keeping with other phase 2 trials of this type and accounts for the possibility of up to 3 drop-outs per arm, which based on previous studies of this type conducted at these sites, represents a conservative estimate of the expected drop-out rate. The statistical analysis plan (SAP) will be developed before the database is locked.

Trial Duration:

37 days (up to 9 days pre-treatment plus 15 days treatment period plus 14 days post-treatment follow-up).

Recruitment period 18 months. Recruitment of additional arm 7 will be 2 months.

1.2 Trial Flow Chart

Period	**Pre-Treatment**			**Treatment**						**Follow-up**	
Visit	**1**	**2**	**3**	**4**	**5 to 10**	**11**	**12 to 16**	**17**	**18**	**Early With-drawal**	**19**
Day	**(-9 to -3)** [A]	**-2** [B]	**-1**	**1**	**2 to 7** [C]	**8**	**9 to 13** [C]	**14**	**15**		**28**
Documentation of Positive GeneXpert/TB smear (TB clinic/site of initial diagnosis)	X										
Written Informed Consent	X										
Demography	X										
Medical & Treatment History	X										
Inclusion/Exclusion/Eligibility Assessment	X		X								
Chest X-ray	X										
Physical Examination [D]	X			X	X	X	X	X	X	X	X
Vital Signs [E]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X										X
PK [F]								X	X	X	
Spot Sputum (confirm TB & adequate bacterial load) [G]	X										
Rifampicin Resistance Test (rapid) [G]	X										
Haematology, Clinical Chemistry, Urinalysis [H]	X			X		X		X		X	X
Urine Drug Screen [I]	X	X [I]									
β-HCG Serum Pregnancy (women of child bearing potential only)	X										
Urine Pregnancy Test [Q]		X	X					X	X		
HIV Test and CD4 Count	X										

Period	Pre-Treatment			Treatment						Follow-up	
Visit	**1**	**2**	**3**	**4**	**5 to 10**	**11**	**12 to 16**	**17**	**18**	**Early With-drawal**	**19**
Day	**(-9 to -3)** [A]	**-2**[B]	**-1**	**1**	**2 to 7**[C]	**8**	**9 to 13**[C]	**14**	**15**		**28**
Urine and Serum Biomarkers[J]				X	X			X		X	
FDG-PET/CT[K]		X	X					X	X		
Hospital Admission	X[B]	X[B]									
Overnight Sputum[L]		X	X	X	X	X	X	X			
Randomization[M]		X	X								
IP Administration and Compliance Check				X	X	X	X	X			
Mycobacteriology Assessments [N]		X						X			
Hospital Discharge									X	X	
Concomitant Medication		X	X	X	X	X	X	X	X	X	X
Adverse Events[O]				X	X	X	X	X	X	X	X
Point of Care Blood Glucose[P]		X	X					X	X		

A: The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible.

B: Participants can proceed with the Visit 2 (day -2) assessments as soon as their Visit 1 (day -9 to -3) assessments have been completed i.e. Visits 1 and 2 may occur on the same day as long as the screening results are available in time for randomization at Visit 3. Participants may be hospitalized during the entire pre-treatment period if the Investigator considers it advisable.

C: All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these times, unless specified differently elsewhere.

D: Height (m) will only be collected once at Visit 1 (day -9 to -3). A full physical examination will be performed at Visit 1 (day -9 to -3), with symptom-directed physical examinations at Visit 17 (day 14), Visit 19 (day 28) and Early Withdrawal. Symptom directed physical examinations may be conducted as required during the study (visits 4 to 16).

E: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg), heart rate (beats per minute [bpm]), body temperature (axillary; oral) and weight (kg). To be performed within 2 hours before the first daily dosing on Visit 4 (day 1) through to Visit 17 (day 14) and within 2 hours before the time dosing would have occurred on Visit 18 (day 15). On days where the following assessments are done the order should be: vital signs before blood draws for PK or safety assessments.

F: PKs will be performed as noted in the PK flow chart. No PK will be performed on the Rifafour e275® treatment arms. At the Early Withdrawal Visit (EWV) a PK will be done pre-dose of the time of the planned first daily dosing. If this is not possible, a random PK sample will be done.

G: Microscopy and molecular rapid test for TB and rifampicin resistance (GeneXpert). If the first spot sputum does not show unequivocal results, the tests may be repeated on freshly collected spot sputum or overnight sputum and that result used.

H: Laboratory assessments: haematology (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count). Clinical Chemistry (albumin, urea, creatinine, direct, indirect and total bilirubin, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactic dehydrogenase (LDH), sodium, potassium, calcium (corrected for albumin), chloride, random/fasting glucose). Urinalysis (pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes, microscopy). To be performed within 2 hours before dosing on Visit 4 (day 1) and Visit 11 (day 8) and within 2 hours before the time dosing would have occurred on Visit 17 (day 14).

I: Urine drug screen: cannabinoids, cocaine, met/amphetamines and opiates. Urine drug screen can be repeated at Visit 2 (day -2) for participants who were not hospitalized at Visit 1 (day -9 to -3).

J: Urine and blood collected for biomarkers at day 1 before the first IP dosing, days 3, 7, 14 and the EWV.

K: FDG-PET/CT will be done on day-2 or day -1 visit, or before IP is administered on day 1. Day 14 FDG-PET/CT has a +/- day 1 window. In the event of an FDG-PET/CT not being able to be done within the allowed window of +1 day, it should be done within +3 days and the IP should be continued until the FDG-PET/CT has been completed.

L: Overnight sputum sampling may start at Screening visit (day -9 to -3) or on Visit 2 (day –2) and will continue daily until Visit 7 (day 4), Visit 9 (day 6), Visit 11 (day 8), Visit 13 (day 10), Visit 15 (day 12) and Visit 17 (day 14). Sputum sampling will stop on the morning of Visit 18 (day 15). Sputum collection will start in the afternoons around 15h00 and continue for 16 hours +/- 1 hour

overnight. The 16-hour sputum sampling for each of the sampling days must be finished prior to the administration of the next day's IP.

Overnight sputum collection may be collected for a number of screening days if the screening results are delayed, or the mycobacterial testing on the first spot sputum shows an indeterminate result, in which case the test may be repeated on a freshly collected spot sputum or an overnight sputum and that result used. It will not be collected for more than the pre-treatment time period. Of the pre-treatment period samples collected only the Visit 2 (day-2) and Visit 3(day -1) overnight sputum samples will be used for the activity endpoint tests.
The day sputum collection starts reflects the day to which that sample applies. e.g. a sample whose collection starts on day 1 and ends on day 2, is designated as the day 1 overnight sputum sample (and results).

M: Randomization by the pharmacist/registered dispenser may occur once all the screening results are available and the Investigator has determined that the participant is eligible for the trial.

N: A culture will be grown from a sputum sample submitted before treatment initiation (baseline) for confirming that the infecting organism is *M. tuberculosis* susceptible to isoniazid and rifampicin (GenoType MTBDRplus, Hain, Nehren, Germany). Cultures from baseline and from day 14 sputum will be kept for determination of the minimum inhibitory concentration (MIC) of the investigational agents that the subject was treated with. If a Day 14 culture is not available the last available culture after Day 8 will be kept. MIC tests for beta-lactams are under development and cultures might be exported for this purpose.

O: Adverse events (AE) will be collected by the Investigator from the time a participant receives his/her first dose of IP through to the Visit 19 (day 28) Follow up Visit.

P: Point of care blood glucose test to coincide with the day of the PET scan and does not have to be repeated on the other days.

Q: The urine pregnancy test at baseline and day 14 has to coincide with the PET scan day and does not have to be repeated on the other days.

1.3 PK Chart

STUDY VISIT	**Visit 17**										**Visit 18**
STUDY DAY	**Day 14**										**Day 15**
STUDY HOUR	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**
Dose	X										
Pharmacokinetic sampling		X	X	X	X	X	X	X	X	X	X

PK samplings are to be performed at the specified time points as follows:

- Pre-dose (study hour 0): 0-5 minutes before first daily dose on day 14 (0 hours)
- 0.5 hour: at 30 minutes post dosing of the first daily dosing on day 14 (+/- 5 min)
- 1 – 6 hours: at 1, 1.5, 2, 3, 4 and 6 hours post dose of the first daily dosing on day 14 (+/- 10 min)
- 8 hours: at 8 hours post dose of the first daily dosing on day 14 (+/- 15 min)
- 12 hours: at 12 hours post dose of the first daily dosing on day 14 (+/- 15 min)
- 24 hours: at 24 hours post dose of the first daily dosing on day 14 (+/- 30 min)

EW = Early withdrawal. PK sampling to be performed pre-dose of the time of the first daily dosing on preceding days.

No PK sampling will be done on the Rifafour e275® control groups

2. Background Information

2.1 Tuberculosis

Tuberculosis (TB) remains a concerning health problem, with *Mycobacterium tuberculosis* (*Mtb*) now causing more deaths than HIV/AIDS. Six countries in Africa and Asia accounted for the majority of the 10.4 million new TB cases reported in 2018 (WHO 2019). The current long-standing first-line antituberculosis agents are relatively ineffective in controlling the TB epidemic in high-burden countries. Treatment takes 6 -9 months to complete and is associated with side effects resulting in poor compliance which leads to treatment failure and an increased likelihood of developing drug-resistance.

Drug-resistant TB poses a major threat to control of the TB epidemic. The prevalence of multi drug resistant TB (MDR: resistance to at least isoniazid and rifampicin) and extensively drug resistant (XDR: MDR plus resistance to at least a fluoroquinolone and an injectable antituberculosis drug) continues to increase. In 2018, an estimated 600 000 new cases qualified for MDR-TB treatment and incident cases of XDR-TB, approximately 10% of patients with MDR-TB, were reported in more countries, including Eastern Europe and India (WHO 2019).

The treatment of DR-TB remains sub-optimal due to constraints such as availability, duration (9-24 months, of which 6 months is an injectable), and significant toxicities leading to poor compliance and an increased risk of developing further drug-resistance. The new 9-month regimen for MDR-TB recently proposed by the WHO is optimising the use of currently known substances but only a minority of MDR cases are likely to qualify for it (WHO 2016b). Despite the lengthy duration, DR-TB treatment is only successful in around half of MDR- and less than a third of XDR-TB cases, further escalating the threat to global health.

The development of new drug combinations that are effective against drug-resistant strains of *Mtb*, and that have the potential to shorten the duration of TB treatments seem to be an effective approach to tackling the TB pandemic. The addition of promising new drugs such as moxifloxacin, bedaquiline (Rustomjee 2008; Diacon 2009; Diacon 2013), delamanid (Diacon 2011b), PA-824 (Diacon 2010; Diacon 2012) and new oxazolidinone candidates (Wallis 2014; Furin 2016) for M/XDR-TB, could help to improve this situation. Questions however remain related to their best possible use in combination regimens. At least three different drugs are needed to construct a new treatment regimen to which no clinical resistance exists, but potential antagonism in humans between agents (Mdluli 2011), for instance PA-824 and bedaquiline, and the additive potential for significant toxicity e.g. QTc prolongation of moxifloxacin (Bloomfield 2008), bedaquiline (Matteelli 2010) and possibly some others, are narrowing down the number of possible combinations. This highlights the need for the development of additional new chemical entities that strike an appropriate balance between antituberculosis activity and safety profiles, a balance that will enable new future drug combinations that make the best of previously developed entities.

2.2 Early Bactericidal Activity Clinical Studies

The assessment of the early bactericidal activity (EBA) of antituberculosis agents in sputum over the first 2 weeks of treatment is the established method for the early clinical evaluation of new antituberculosis agents and regimens (Jindani 1980). The primary endpoint of EBA studies is the daily rate of change of colony forming units (CFU) of *Mtb* in sputum (measured as $\log_{10}$CFU/ml sputum/day) or the prolongation of time to positivity (TTP) in liquid culture (measured in hours/day) in untreated patients with smear-positive pulmonary tuberculosis (TB). The latter provides an indication whether a novel treatment has antituberculosis properties in humans, and gives an early indication of the dosage required. Pharmacokinetic analyses offer the opportunity to study the relationship between dosages, serum levels, efficacy and other host or pathogen factors related to the compound. Preliminary safety and tolerability data can also be collected for the duration of the treatment (Donald 2003; Diacon 2011a).

2.3 New Biomarkers as Surrogates for Drug Activity

EBA studies also allow the exploration of new ways of measuring TB treatment activity in short-course trials beyond measurement of CFU or TTP. Such novel surrogate markers can be radiological, immunological, biochemical, microbiologial or any combination of these. In addition to more traditional biomarkers from urine or blood, an interesting candidate is Positron Emission Tomograpy (PET) as a non-invasive approach to evaluate drug action by measuring the activity of inflammation in lung tissue. PET with 2-[18F]-fluoro-2-deoxy-D-glucose ([18F]-FDG) integrated with computed tomography (CT) is a non-invasive imaging technique widely used as a clinical diagnostic tool, especially in the field of oncology. The [18F]-FDG tracer is taken up by cells with increased metabolic activity and a greater need for glycolysis, resulting in increased expression of glucose transport proteins and up-regulation of intracellular hexokinase and phosphofructokinase. Once these cells take up [18F]-FDG, it is phosphorylated and "trapped" within the cell. The concentration of tracer within a particular region of interest can then be quantified (Kaim 2002; Hara 2003; Harkirat 2008). Novel biomarkers that reflect the early treatment-induced changes could significantly impact future clinical trial design, and shorten clinical development timelines.

2.4 Optimizing the Use of Existing Antibiotics

There are two approaches that can be taken to develop new treatments for both drug-sensitive TB and drug-resistant TB. The first, and ideal, is the development of new chemical entities (e.g. bedaquiline and delamanid) with novel mechanisms of antituberculosis activity, but without the possibility of cross-resistance to existing antimycobacterials. The second approach to finding new TB treatment options is repurposing of existing antibiotics with known pharmaceutical properties that are currently approved for other conditions, or boosting efficacy of known TB drugs (e.g. rifampicin) through potentiation of its activity by combination with a synergistic partner drug.

2.5 Agents to be Studied

2.5.1 Repurposing an Optimised Combination of Beta-lactams for MDR/XDR-TB

The beta (β)-lactams are a broad family of antibiotics that include the penicillin derivatives, cephalosporins, monobactams, carbapenems, and the β-lactamase inhibitors. The β-lactams have an exceptional track record of clinical safety in humans and has been in widespread use for many decades. The β-lactam antibiotics act by inhibiting bacterial cell wall synthesis by binding to and inactivating peptidoglycan 4→3 cross-linking enzymes of classical D,D-transpeptidase – the penicillin binding proteins (PBPs) (Goffin 1998).

Despite being successful antibiotics, the β-lactams have historically been overlooked as candidates for TB treatment. The general perception was that β-lactams are ineffective against *Mtb* due to rapid hydrolyses by *Mtb's* chromosomally encoded, broad spectrum β-lactamase, BlaC. Clavulanic acid (CA) functions as a β-lactamase inhibitor by quickly binding to *Mtb* Blac, stably and irreversibly deactivating the enzyme (Hugonnet 2007). CA itself has no significant antimicrobial activity and is marketed for human use only in combination with amoxicillin and ticarcillen for the treatment of certain bacterial infections. The addition of CA enhances the activity of other β-lactams (Finlay 2003). In combination with CA, the *in vitro* bactericidal activity of amoxicillin against *Mtb* is improved (Cynamon 1983; Chambers 1998).

The carbapenems are the β-lactams with the broadest spectrum of activity and they are poor substrates for BlaC, exhibiting rapid acylation followed by slow deacylation, enabling them to also act as potent inhibitors of BlaC (Tremblay 2010). This was demonstrated *in vitro* for the interaction of BlaC with meropenem (Hugonnet 2009) and also ertapenem (Tremblay 2010). It has recently been demonstrated that the majority of *Mtb's* peptidoglycan cross-links are of the 3→3 type that are catalysed by nonclassical L,D-transpeptidases critical for cell wall biosynthesis. These nonclassical transpeptidases are innately resistant to the earlier generation β-lactams, but are efficiently inactivated by the carbapenems; by imipenem and ertapenem more rapidly than by meropenem and doripenem (Gupta 2010; Dubee 2012; Cordillot 2013; Lun 2014; Kumar 2016). There are five genetic variants of L,D-transpeptidases, designated Ldt_{Mt1} to Ldt_{Mt5} with both Ldt_{Mt1} and Ldt_{Mt2} inactivated by carbapenems *in vitro* (Tipper 1965; Lavollay 2008). The nonclassically cross-linked peptidoglycan has also been reported to predominate in non-replicating *Mtb,* or persisters, with Ldt_{Mt1}

thought to play a critical role in peptidoglycan adaptation to the non-replicating state of *Mtb* (Lavollay 2008). The loss of the gene that encodes L,D-transpeptidases for 3→3 cross-linking results in altered cellular morphology and size of *Mtb*, loss of virulence and increased susceptibility to amoxicillin/CA during the chronic phase of infection, both *in vitro* and in a mouse model of TB. This suggests that a drug that inhibits both L,D-transpeptidase and β-lactamase could effectively treat chronic persisters of *Mtb* (Gupta 2010), an attractive approach to development of anti-TB drugs.

2.5.2 Preclinical Rationale for Use of ß-lactams for Tuberculosis

Contrary to the perceived intrinsic resistance of *Mtb* against β-lactams, there has been longstanding proof that amoxicillin, alone and in combination with CA, has *in vitro* activity against *Mtb* (Cynamon 1983; Chambers 1998). When CA was combined with meropenem, potent bactericidal activity against laboratory strains of *Mtb* was achieved. Sterilization of aerobically grown cultures was observed within 14 days. Inhibitory activity against anaerobically grown cultures that mimic the "persistent" state was seen and the combination also inhibited the growth of 13 extensively drug-resistant strains of *Mtb* (Hugonnet 2009). The activity of meropenem is further potentiated by amoxicillin/CA. Gonzalo and colleagues confirmed the synergy of meropenem and amoxicillin/CA by conducting experiments with 28 *Mtb* strains (7 susceptible, 2 mono-resistant, 16 MDR and 3 XDR) that were tested against different concentrations and combinations of meropenem, CA and amoxicillin. All of the strains resistant to high concentrations of amoxicillin increased their susceptibility to amoxicillin/CA after the addition of meropenem. The addition of CA to meropenem reduced the minimum inhibitory concentration (MIC) of meropenem by an average of over 1.8 dilutions. The authors concluded that the combination of amoxicillin/CA plus meropenem is active against *Mtb* strains including MDR/XDR-TB strains *in vitro* (Gonzalo 2013) (Figure 1). These results were also reproduced in a murine model of tuberculosis (Veziris 2011; England 2012).

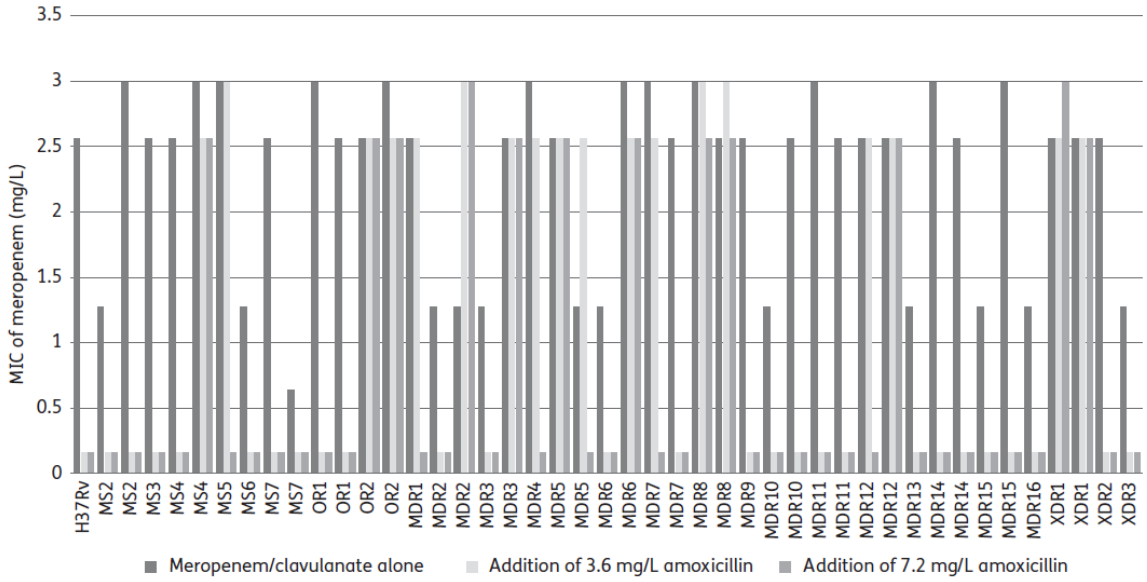


Figure 1 : MIC of Meropenem in the Presence of a Fixed Concentration of 2.5mg/l CA before and after the Addition of Amoxicillin (Gonzalo 2013)

Ertapenem is a newer carbapenem with a longer half-life than imipenem and meropenem. The data in support of ertapenem as a promising β-lactam option with clinical anti-TB activity is less than with meropenem. Like meropenem, ertapenem is also a slow substrate for *Mtb* BlaC and acts as an inhibitor of BlaC *in vitro* (Tremblay 2010). In an *in vitro* peptidoglycan cross-linking assay, ertapenem inactivated the Ldt_{Mt1} paralogue of *Mtb* L,D-transpeptidases more rapidly than meropenem (Cordillot 2013). England and colleagues reported on the intracellular susceptibility of *Mtb* to carbapenems, including ertapenem, in combination with 200μM CA. Highly significant killing was observed for all carbapenems by day 2 with a 1.5 to 2.0 log reduction in CFU compared to untreated controls at day 6 (Figure 2) (England 2012). In a murine model of TB, imipenem and meropenem in combination with CA, significantly improved survival of mice, but was not bactericidal. The MICs of imipenem, meropenem,

and ertapenem against Mtb in the presence of CA were reduced 4-16 fold (Table 1). The MIC of ertapenem/CA did not fall in the range of susceptibility and ertapenem was also less effective at preventing mouse mortality. It is, however, important to keep in mind that the half-life of ertapenem in mice is shorter than in humans (1 hour in mice versus 4 hours in humans). The antibacterial activity of the β-lactams depends on the time above MIC, and the author concluded that the activity of ertapenem in the model is probably less than can be expected in humans (Veziris 2011).

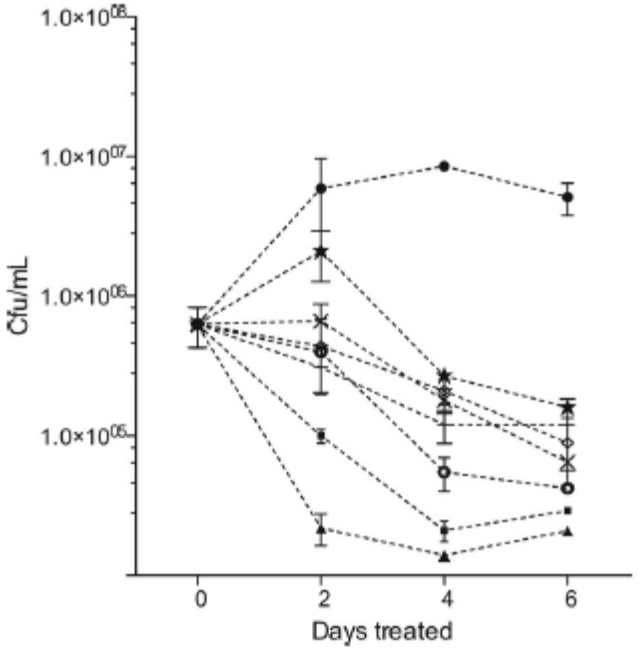


Figure 2: Intracellular Susceptibility of H37Rv to Carbapenems in Combination with CA (England 2012)
●, untreated controls; ■, rifampin; ▲, isoniazid; x, meropenem; ◊, faropenem; +, doripenem; ✦, ertapenem; ○, imipenem.

Treatment	**MIC H37v μg/ml**		
	-	2.5μg/ml CA	EUCAST susceptibility breakpoints
Imipenem	16	1	2-8
Meropenem	8	1	2-8
Ertapenem	16	4	0.5-1

Table 1 : MICs of Imipenem, Meropenem, and Ertapenem Alone and in the Presence of 2.5μg/ml of Clavulanate (Ca) (Veziris 2011)

Treatment	**MIC H37v μg/ml**	
	-	2.5μg/ml CA
Amoxicillin (Hugonnet 2009)	>10	>10
	-	8μg/ml CA
Amoxicillin (Chambers 1998)	>16	≤2

Table 2: MICs of Amoxicillin

The MIC for Mtb of CA alone is >64μg/ml (Ramon-Garcia 2016).

Following insights from preclinical testing there was ample reason to believe that the carbapenems could be repurposed as therapeutic agents for TB (drug-resistant and drug-sensitive) when enhanced

with other blockers of β-lactamase (Hugonnet 2009). Furthermore, a regimen that contains an inhibitor of, both L,D-transpeptidases and β-lactamase, in combination with a β-lactam may be able to kill replicating and non-replicating *Mtb* bacilli by destroying the peptidoglycan layer.

2.5.3 Clinical Rationale for Use of ß-lactams for Tuberculosis

The β-lactam antibiotics have been proposed as antituberculosis agents and tested clinically. Amoxicillin/CA has been evaluated in two EBA studies. In the first, 10 pulmonary tuberculosis participants from the USA and Turkey received amoxicillin 1g with CA 250mg three times daily for 7 days and a reasonable 2-day EBA of 0.39 logCFU/ml/day (SD 0.32) was found, although EBA days 2-7 fell to 0.02 (SD 0.04) (Chambers 1998). A later study from Cape Town enrolling 10 participants to receive amoxicillin 3g and CA 750mg in a single dose, found a 2-day EBA of only 0.018 (SD 0.130) that did not differ from that found in participants receiving no drug (0.016, SD 0.069) (Donald 2001). The reason for these conflicting findings is unclear.

Yew *et al*. reported in 1995 their experience with 5 participants with MDR-TB in whom amoxcycillin/CA was part of the treatment regimen. The contribution of amoxicillin/CA to the overall effectiveness of the multidrug regimens described in that report is unknown. Two out of 5 participants eventually achieved sustained culture conversion. No gastro-intestinal, biochemical or haematological side effects were noted (Yew 1995).

2.5.4 Clinical Rationale for Use of Carbapenems for Tuberculosis

Intravenously applied meropenem/CA has repeatedly shown antituberculosis activity in humans. Case series have documented positive results with intravenous meropenem with or without CA in therapeutically destitute participants with highly drug resistant tuberculosis. Dauby et al reported successful treatment of a 14-year old female by adding intravenous meropenem 1.5 g thrice daily, and amoxicillin 1g/CA 200mg thrice daily, to a regimen of capreomycin, linezolid, clarithromycin, pyrazinamide and cycloserine. No adverse events from the ß-lactam combination were noted (Dauby 2011). Six Participants aged 14-46 years with XDR TB (1 HIV-positive) were treated with 4-6g of meropenem administered intravenously twice or three times daily and with CA given in the form of a combination of amoxicillin plus CA (500 mg/125 mg), in addition to individual background regimens with other drugs. Dramatic improvement was found in 5 of 6 participants with the majority proceeding to cure or successful surgery. No adverse reactions were attributed to meropenem-amoxicillin-CA (Payen 2012). In the largest series to date the retrospective efficacy and safety of meropenem/CA added to linezolid-containing regimens in the treatment of MDR- and XDR-TB was reported. Meropenem/CA (3 g daily dose) was prescribed to 37 cases with MDR-/XDR-TB. Treated cases exhibited higher smear- and culture-conversion rates than controls. One case had to withdraw from meropenem/CA due to increased transaminase levels. Five (13.5%) participants experienced diarrhoea potentially attributed to meropenem–CA but this did not require withdrawal of the drug (De Lorenzo 2013).

In a recent successful proof-of-concept study, we found robust 2-week bactericidal activity of intravenous meropenem, administered at maximum allowable dosage of 2g thrice daily, in combination with oral amoxicillin/CA (500mg/125mg) thrice daily. 15 Participants were randomized to receive the meropenem-amoxicillin/CA combination while 15 were randomized to receive a standard oral anti-TB regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) once daily. We found an average daily fall in CFU of *Mtb* per ml sputum of 0.11 (95% confidence interval [CI], 0.09 to 0.13) and 0.17 (95% CI, 0.15 to 0.19) for the meropenem-amoxicillin/CA and HRZE arms respectively ($p<0.001$ for both groups, as compared with no effect; $p<0.001$ for the comparison between groups) (Figure 3). The reduction of CFU during the first 14 days of treatment is comparable to that previously reported for rifampicin and pyrazinamide. Adverse events, mostly diarrhoea, were mild and infrequent. It was unfortunate that no activity was detected for the orally available alternative carbapenem, faropenem sodium, also evaluated in the aforementioned EBA. Faropenem has shown efficacy in a murine model of TB when combined with amoxicillin, clavulanate and probenicid (Rullas 2015), but it is possible that no EBA was detected in the study due to low levels of exposure and limited time above the MIC for faropenem (Diacon 2016).

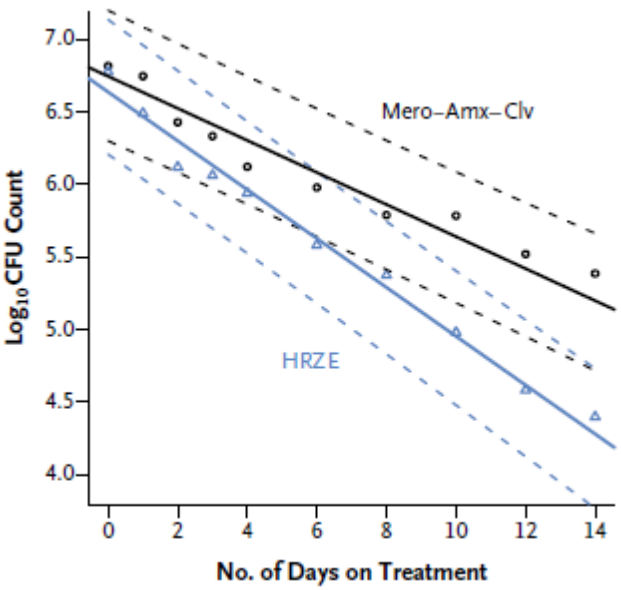


Figure 3 : Estimated log_{10}CFU Counts per Treatment Over Time

The figure shows mean log10 CFU counts at each time point as symbols (triangles and circles) and superimposed treatment activities as lines, with 95% confidence intervals shown as dashed lines, as derived from a linear mixed-effects model (Diacon 2016).

Following the successful POC, we conducted the second EBA study described in this protocol with the aim to simplify carbapenem treatment for TB. We evaluated the 14-day EBA of meropenem combined with oral amoxicillin/CA in participants with rifampicin susceptible pulmonary TB. Participants received meropenem 6g once daily administered intravenously over 6 hours along with two tablets of amoxicillin/CA 1000/62.5mg 12 hourly (Group 1, arm 1). In the interim analysis, linear mixed-effects modelling was used to estimate the EBA as the daily change in log_{10}CFU per ml sputum. A total of 18 participants were enrolled in the meropenem group (participants who withdrew were replaced) and 4 in the HRZE control group. Mero-Amx/CA 6g once daily showed significant EBA with a daily decrease of 0.094 (95% CI: 0.075 to 0.115, p-value<0.0001) which was not different from mero-amx/CA 2g 8-hourly in the POC (Figure 4). The higher dosage of meropenem was well tolerated without toxicity (De Jager 2020).

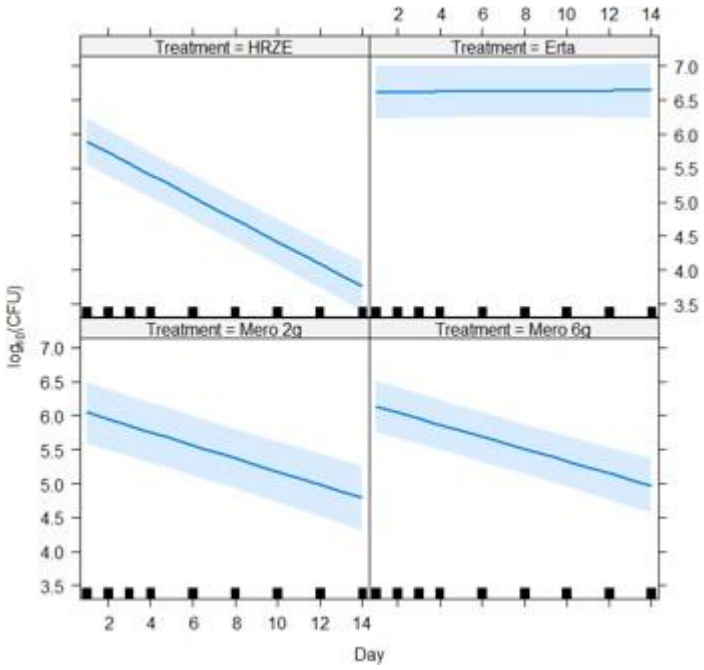


Figure 4 : **Estimated log10CFU Counts per treatment over time for meropenem 6 grams once daily over 6 hours**

This figure shows the fourteen-day mycobactericidal activity of intravenous meropenem 6 grams once daily over 6 hours vs. 2 grams 8-hourly, compared to that of ertapenem 1 gram once daily intramuscularly and HRZE dosed once daily according to standard weight bands. The darker blue lines represent estimated daily on-treatment log10(CFU), adjusted for baseline CFU, age, BMI, gender and study. The lighter blue shadows are the associated 95% confidence bands. The dark squares represent time point of sputum collection. We employed a single joint linear mixed-effects model, taking into account the correlation between observations from each participant.

HRZE = isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). CFU = colony forming units. BMI = body mass index. Erta = ertapenem. Mero = meropenem.

The antituberculosis activity of ertapenem has not yet been formally studied in humans. Tiberi *et al.* were the first to report on ertapenem when used as part of a multi-drug regimen to treat a small number of patients with MDR-TB in Italy. Safety, tolerability, and efficacy data of ertapenem was retrospectively collected on MDR-TB cases treated between 2008 and 2015. Carbapenems were incorporated into regimens when background agents were failing and included meropenem (3g thrice daily) and imipenem (500mg 4 times a day) for inpatient treatment. Ertapenem 1g once daily was the carbapenem of choice for easier home or day-hospital administration. Three out of 5 patients who were treated with an ertapenem-containing regimen were considered cured at end of treatment and 1 participant improved clinically, but sputum cultures did not convert to negative. All the carbapenems were well tolerated (Tiberi 2016). In The Netherlands 18 patients with drug resistant TB were treated with a multi-drug regimen that contained ertapenem. Safety and pharmacokinetic data was collected retrospectively. All of the 18 patients who received 1g ertapenem intravenously once daily for a mean of 77 (5-210) days had conversion of sputum smears and cultures to negative. Fifteen of the 18 participants completed treatment and were considered cured. Ertapenem was well tolerated with a favourable pharmacokinetic/ pharmacodynamics profile (Van Rijn 2016). Given the fact that ertapenem can be administered once daily intramuscularly and, along with its good safety profile, it seems to be a promising β-lactam for MDR-TB treatment that warrants further investigation in prospective clinical trials.

From the interim analysis described in this protocol, we found that intramuscular administration of Ertapenem 1g daily with two tablets of amoxicillin/CA 1000/62.5mg 12 hourly does not have an EBA (Figure 4). The results of the group 2 analysis are pending at the time of writing this amendment.

2.5.5 Boosting the Activity of Rifampicin

Rifampicin is a key drug in standard TB treatment. Its introduction, together with pyrazinamide, has allowed shortening of treatment duration from 18 to 6 months (Fox 1999). The standard 10mg/kg (600mg) dose of rifampicin has been used for years and selection of this dose was made based on "favourable" pharmacokinetics and concerns about adverse events, but primarily to cut costs (Van Ingen 2011). To the contrary, studies with higher than standard doses of rifampicin have consistently shown a direct relationship between the dose administered and antituberculosis activity as well as safety (Diacon 2007; Steingart 2011). Boeree and colleagues reported on a dose-ranging trial of rifampicin in participants with pulmonary TB (PTB). 10 Participants received standard 10mg/kg rifampicin and 15 participants per experimental arm were randomized to receive 20, 25, 30, and 35mg/kg rifampicin, respectively, over 14 days. High-dose rifampicin at 35mg/kg resulted in clinically relevant increases in systemic drug exposure and showed a greater estimated fall in bacterial load over 2 weeks. The higher dose was also safe and well tolerated (Boeree 2015). In a more recent multi-arm, multi-stage trial by the PanACEA consortium, rifampicin 35mg/kg was administered to participants with PTB in combination with ethambutol, isoniazid and pyrazinamide over a 12-week intensive phase treatment period. The higher dose was safe, well tolerated and showed to be more efficacious in terms of culture conversion in liquid media than a control arm receiving standard HRZE (Boeree 2017). Though the maximum dose of rifampicin has not yet been identified, there are likely limits to its oral bioavailability, and exposure levels needed to overcome rifampicin resistance are not achievable (Boeree 2015). One alternative to boost rifampicin activity is potentiation by combining it with a synergistic partner (Ramȯn-García 2011).

The intrinsic resistance of *Mtb* to most clinically approved antibiotics led Ramȯn-García and colleagues to test whether certain available antibiotics with limited efficacy against *Mtb* might be repurposed as anti-TB drugs when administered in combination with a synergistic partner drug. A high throughput screen (HTSS) was developed and an in-house library of around 600 commercially available antibiotics, most with unknown activity against *Mtb*, was screened for synergistic activity with rifampicin. Synergistic activity was validated through checkerboard assays (Ramȯn-García 2011). A large proportion of cell wall inhibitors, mainly the β-lactams, were identified as hits with rifampicin. One possible explanation for the synergy could be that the β-lactams target the peptidoglycan layer of the cell wall causing increased permeability and thus intracellular accumulation of rifampicin. In combination with amoxicillin, with and without CA, the carbapenems tested had a range of effects on rifampicin accumulation. The largest effect was, however, elicited by the amoxicillin/CA combination. On average the synergism between the β-lactams and rifampicin allowed up to a 16-fold reduction in the MIC of rifampicin. Clavulanic acid was found to be a key partner in triple synergistic combinations that were effective against rifampicin-resistant strains of *Mtb* (Ramȯn-García 2016). Promising *in vitro* synergistic activity of amoxicillin/CA with rifampicin was also reported by Pagliotti and colleagues, whose study also demonstrated no antagonism between amoxicillin/CA and other first line TB drugs i.e. isoniazid and ethambutol (Pagliotti 2016). The addition of CA could therefore further enhance the anti-tuberculosis activity of rifampicin/β-lactam combinations (Ramȯn-García 2016).

2.6 Known and Potential Risks and Benefits of the Investigational Product/s and Procedures

2.6.1 Beta-lactams

Beta-lactams are widely available, approved for human use and free of QTc-prolongation or potential interactions with current antituberculosis drugs and antiretroviral agents, making them suitable candidates for use in combination treatment regimens in patients with drug-resistant TB. Meropenem, ertapenem as well as amoxicillin/CA are marketed drugs from the β-lactam class that has an

exemplary safety record (Linden 2007). Though not tested in this study all the beta-lactams are available in paediatric formulations. Further information is provided in the accompanying documentation.

2.6.2 Amoxicillin/CA

The most common side effects experienced are diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness and hot flushes.

2.6.3 Carbapenems

To date, the most frequently observed (>2%) side effects from clinical trial of Meropenem IV (as per package insert) are categorised into local adverse reactions and systemic adverse reactions. Local adverse reactions include inflammation at the injection site, pain at the injection site, oedema at the injection site and thrombophlebitis. Systemic adverse events include headache, nausea, constipation, diarrhoea, anaemia, vomiting, skin rash pruritis, apnea, sepsis and shock.

The most frequently observed adverse experiences reported in clinical trials of ertapenem (as per package insert) were diarrhoea, injection site reactions, nausea, headache, and vaginitis in females. These adverse events were described as mild to moderate in severity.

2.6.4 Rifampicin (35mg/kg)

Studies have shown that rifampicin used at higher than standard dose were safe and well tolerated. In the trials with high-dose rifampicin monotherapy, the most common adverse events reported were abdominal pain, vomiting, headache, and pruritis. When used in combination with isoniazid, pyrazinamide, and ethambutol additional adverse effects such as hyperuricemia, and pain in the extremities occurred in all groups and were not attributable to a specific dose group (Boeree *et al*. 2015).

2.6.5 Rifafour e275®

Some participants will be treated with standard, intensive phase pulmonary TB treatment as recommended in the SA National TB Treatment Guidelines as a positive control to verify that the laboratory assays used measure the expected magnitude of activity. This is RHZE 150/75/400/275 mg oral daily (Rifafour e-275®) (HRZE: H=isoniazid: R=rifampicin: Z=pyrazinamide: E=ethambutol). The Rifafour treatment group is included as a control for the EBA quantitative mycobacteriology and to evaluate whether HRZE in this population gives similar EBA results to that demonstrated in prior studies with this combination.

Please see the Rifafour e-275® Package Insert for its known and potential risks and benefits.

2.6.6 Blood Draws and Sputum Collection

There are minor risks related to blood drawing, including discomfort, haematoma, and rarely an infection. Sputum collection may also be uncomfortable and sputum induction can cause wheezing or a tightness in the airways. It is generally thought to be a safe procedure. There is a risk, although rare, that placing an IV for the administration of IP or for the FDG-PET may result in a hematoma, thrombophlebitis, infection, or nerve damage.

2.6.7 FDG-PET/CT Scans

There is also risk associated with radiation exposure from imaging. Radiation from CXR is negligible. Both PET and CT components of the scan will expose subjects to ionizing radiation. We have considered ways to limit the amount of radiation exposure subjects will receive. By restricting the CT scan to the chest as the area of interest rather than performing a whole body scan (which is customary for PET/CT) we will reduce radiation exposure and reduce incidental findings. Also by limiting the number of subjects that receive more than one PET/CT scans we will limit total radiation exposure of the cohort. Subjects will undergo a maximum of 2 PET/CT scan in a calendar year during the course of the study. The expected maximum effective dose a subject will receive from scans and CXR

scheduled as part of the study over one calendar year is 3.14 rem. The breakdown is as follows when 7 mCi of F-18-FDG is injected per subject for each PET scan:

cScan	Individual Dose (rem)	Maximum Number of Scans Given on Study	Total Dose (rem)
CXR	0.04	1	0.04
FDG-PET	0.44	2	0.88
CT	1.11	2	2.22
TOTAL Maximum ED			**3.14**

Table 3: Total Maximum Radiation per Subject Per 1 Year (3 PET/CTs and 1 Chest X-ray)

This is less than the maximal permissible annual occupational exposure of 5 rem/yr (USNRC 2004) .

2.7 Overall Benefit/Risk Assessment

Carbapenems have demonstrated substantial *in vitro* and also recent clinical antituberculosis activity against *Mtb*. It is important to establish whether these agents at optimized dosages and given as monotherapy demonstrate promising mycobactericidal activity in the setting of a carefully controlled EBA study.

The risks of each of the investigational agents over a 14 day period are expected to be relatively minor for this period of dosing. The results of this study will establish whether one or several of the drugs have activity, tolerability and safety adequate to take into subsequent studies of longer duration or incorporation into a novel regimen to be used as rescue treatment for XDR-TB.

Participants in this study will be given drugs for 14 days that are not proven for the long term treatment of pulmonary TB. However these drugs are very likely to have anti-TB activity and a delay of treatment with the full standard regimen of 14 days is not expected to have an adverse impact on the ultimate cure of TB in these participants. Participants in this study will have their TB infection carefully characterized and drug sensitivity profiles established. Participants will remain under constant medical attention and will be housed and monitored in hospital from admission through the duration of the treatment period; this will allow a continuous monitoring of the health conditions of each participant, 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. Upon discharge, the participants will be given the initial doses of standard TB treatment and immediately referred to the national TB treatment program local TB clinic. The Investigators' primary responsibility is to ensure participant safety.

3 Trial Rationale and Objectives

3.1 Study Rationale

This trial seeks to establish the antituberculosis effect of the selected agents on serial CFU counts of *Mtb* in sputum over 14 days of therapy. Given the increasing need for novel regimens to treat participants with DS TB, it is important to evaluate the antituberculosis activity of promising anti-TB drugs in a carefully conducted EBA study to determine their contributions as building blocks for potential future studies of new regimens. The results of this study will be used to plan future studies of longer duration.

We recently found robust 2-week antituberculosis activity for meropenem and amoxicillin/CA in tuberculosis patients in a 14-day EBA study. This was the first formal proof, half a decade after the discovery of this drug class, that beta-lactam antibiotics can be used for the treatment of tuberculosis. Based on pharmacokinetic/pharmacodynamic modelling derived from these results we now aim to refine the application of this treatment.

In the 2-week EBA study described in this protocol (TASK-003), we were utilizing once daily 6g meropenem administered as an intravenous infusion over 6 hours with oral amoxicillin/CA twice daily (group 1, arm 1). From the results of the interim analysis following completion of group 1, we now have reason to believe that a once daily dosing regimen is possible. Following proof that a once daily administration of meropenem with oral amoxicillin/CA has bactericidal activity comparable to the 2g intravenous meropenem administered thrice daily in the POC (Diacon 2016), we now aim to refine the administration of meropenem further by shortening the infusion time to one hour by adding an additional meropenem arm to group 2. We fixed the one hour infusion time as the duration and with using either 4g or 6g of meropenem we will have a range of exposures that can be used in a pharmacokinetic modelling analysis.

The antituberculosis activity of ertapenem has not yet been formally studied in humans. Ertapenem can be administered once daily by intravenous or intramuscular injection, making it a more feasible carbapenem option if proven to be successful.

With this study we will evaluate whether the antimycobacterial activity of higher than standard dose rifampicin is enhanced when combined with amoxicillin/CA based on the concept of synergistic activity.

A once daily dosing regimen would make carbapenem treatment accessible for outpatients and hence for the majority of people suffering from drug-resistant tuberculosis in less affluent regions of the world. Shortening the meropenem infusion time from 6 hours to 1 hour will make the administration of meropenem even more suitable for outpatient use. Also, most clinics are familiar with once daily intramuscular injections as part of currently available treatment regimens containing aminoglycosides. The use of amoxicillin/CA in synergistic combination with rifampicin could potentially increase the efficacy of rifampicin which could lead to a shortened DS-TB regimen and allow the re-introduction of rifampicin for MDR-/XDR-TB treatment.
The 14 day duration of the dosing in this study is generally accepted as the longest period that a new drug or regimen may be used in participants with TB in monotherapy.

3.2 Study Design Rationale

This study will be a standard 14 day EBA design incorporating 2 groups with parallel treatment arms. This design allows comparison of the results of this study with similar prior studies of treatments for TB.
No placebo treatment is included in this study – all participants will be given either active study treatment or Rifafour e275® 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.

All participants will remain under constant medical attention and will be housed and monitored in hospital from check-in through the duration of the treatment period; this will allow a continuous monitoring of the health conditions of each participant, 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. Upon discharge, the participants will be given initial doses of standard TB treatment and immediately referred to the national TB treatment program local TB clinic. The Investigators' primary responsibility is to ensure participant safety.

3.3 Rationale for Selection of Agents and Doses

The selection of β-lactam agents and drug doses for this study is based on pre-clinical evidence of β-lactam antimycobacterial activity and the recent demonstrated EBA of a meropenem and amoxicillin/CA combination as well as informal evidence of the success of ertapenem, when added to MDR-/XDR-TB regimens.

In the 2-week proof-of-concept study we were utilizing maximum allowable doses of thrice daily 2g meropenem (short 5 minutes IV infusion leading to high maximum serum concentrations). This treatment could be used as part of a rescue regimen in patients with highly resistant TB for whom no other options exist. However, this treatment is strictly intravenous and can only be given to patients

admitted to hospitals with advanced nursing care. Such facilities are not frequently found in areas where patients with highly resistant TB reside. Based on recent modelling simulations by our group, we now hypothesise that prolonging infusion time will allow us to extend dosing intervals of meropenem or even achieve sufficient exposure with only one infusion. From the results of the interim analysis of once daily meropenem administered as a 6 hour infusion, we now believe that prolonging the infusion time, as well as increasing the dose, successfully increases the percentage of the dosing interval that free drug concentration remains above the MIC (TMIC). TMIC is the main driver of pharmacodynamics correlating with anti-tuberculosis response of β-lactams like meropenem (Macvane 2014). From further pharmacokinetic modelling work done by our group, we now propose that infusion of a higher dose of meropenem over 60 minutes, might make an even more practical once daily dosing regimen possible. Meropenem has been used for outpatient treatment of infective exacerbations of bronchiectasis as a 3g once daily dose administered over 30 minutes intravenously (Darley *et al*. 2000). Bulik and colleagues reported on the use of meropenem as a 3g infusion over 3 hours thrice daily for the treatment of cystic fibrosis (total daily dose of 9g). This higher dosage was well tolerated without toxicity. A concerning but infrequent adverse event of the carbapenems is the development of seizures. Meropenem has a low propensity for neurotoxicity and this likelihood can seemingly be further reduced by administering a high dosage over a longer infusion time thus avoiding high peak concentrations (Bulik et al. 2010). In the POC study conducted by Diacon and colleagues (Diacon 2016), the 2g meropenem dosage was administered over a 5 minute intravenous push leading to high peak serum concentrations. Modelling work performed by our group predicts that the higher dose of 4g or 6g meropenem to be infused over one hour, as is proposed in this amendment, will not lead to higher peak serum concentrations than in the POC study, hence not posing the risk of neurotoxicity (Muliaditan and Della Pasqua, unpublished 2019).

Ertapenem has regulatory approval in South Africa for other non-TB indications. It is used in clinical practice at a dosage of 1g intravenously administered over 30 minutes or 1g intramuscularly, and is generally well tolerated. Ertapenem has been successful when used clinically at the approved dose of 1g daily IV/IM as part of drug-resistant TB regimens.

This protocol tests two beta-lactam treatment options with widely available agents that can potentially be given once daily. If they are active, these treatment options may be helpful for patients that cannot be admitted as inpatients but for whom outpatient or day-care treatment is possible. These two treatments are thus prioritized in this study and will be tested first together with half of the positive control subjects.

The dose of amoxicillin/CA (1000mg/62.5mg), 2 tablets twice daily, is registered in South Africa for use in non-TB infections. Amoxicillin/CA is used widely in routine clinical practice and has a good safety record. In this study it is used primarily for the β-lactamase inhibitory activity of CA because CA is not available for human use on its own. However, the addition of amoxicillin to carbapenems and also rifampicin has been shown to be synergistic (Gonzalo 2013, Ramȯn-García 2016). In the proposed amendment, amoxicillin/CA (1000mg/62.5mg), 2 tablets will be administered once daily to coincide with the once daily administration of meropenem. By including an amoxicillin/CA only treatment arm we will gain understanding of the individual contribution of high dose amoxicillin/CA in all the proposed injectable treatment arms, and we will once and for all settle the question whether amoxicillin/CA has early bactericidal activity or not as earlier trials were not conclusive in this respect (Chambers 1998, Donald 2001).

The selected dose of rifampicin 35mg/kg to be used in this study is based on recent clinical trials in drug-sensitive TB which showed that the higher dose of rifampicin is safe and well tolerated (Boeree 2015; Boeree 2017). Furthermore, the EBA of rifampicin 35mg/kg measured higher than that of the standard 10mg/kg dose (Diacon 2007).

All agents will be sourced locally. Meropenem, ertapenem, and amoxicillin/CA or any of the generic products available in South Africa will be used during the trial. This will depend on availability of the products.

3.4 Exploratory Biomarkers

Through PET/CT and the collection of immunological samples, this protocol will explore new ways of measuring TB treatment activity beyond the measurement of sputum CFU or TTP. By capturing dynamic immunologic markers, in addition to functional and anatomical changes measured by PET/CT, our biologic characterization of durable treatment effects within potentially persistent *M.tb* subpopulations may be expanded. PET is subject to the availability of this resource at the time this study will be conducted. A second PET scanner is planned to be installed in the near future at an academic centre in close proximity to the study site. PET scanning is an exploratory component and not essential to this study and might not be conducted if the resource is not available.

3.5 Trial Objectives

The overall objective of this study is to evaluate the 2-week bactericidal activity and pharmacokinetics of the following beta-lactam containing combinations with the aim to select the most active and implementable solution to be incorporated into a drug-resistant TB combination regimen:

- Once or twice daily meropenem administered intravenously in combination with once or twice daily oral amoxicillin/clavulanic acid;
- Once daily ertapenem administered intravenously and intramuscularly in combination with twice daily oral amoxicillin/clavulanic acid;
- Twice daily oral amoxicillin/clavulanic acid;
- Once daily rifampicin administered orally at highest currently established dosage of 35mg/kg in combination with twice daily oral amoxicillin/clavulanic acid.

3.5.1 Primary Objectives

- Among participants with drug-sensitive pulmonary TB caused by *Mycobacterium tuberculosis:* to estimate the 14 day early bactericidal activity based on colony forming unit counts, of the combination of meropenem with amoxicillin/clavulanic acid, ertapenem with amoxicillin/clavulanic acid, amoxicillin/clavulanic acid alone, and rifampicin with amoxicillin/clavulanic acid;

- Among participants with drug-sensitive pulmonary TB caused by *Mycobacterium tuberculosis* : to estimate the 14 day early bactericidal activity based on time to positivity in liquid culture, of the combination of meropenem with amoxicillin/clavulanic acid, ertapenem with amoxicillin/clavulanic acid, amoxicillin/clavulanic acid alone, and rifampicin with amoxicillin/clavulanic acid.

3.5.2 Secondary Objectives

- To estimate the 2-day, 7-day, and day 2-14 antimycobacterial activity in terms of colony forming units and liquid culture time to positivity;

- To describe the safety and tolerability of the study regimens administered for 14 days;

- To determine the steady state pharmacokinetic parameters of meropenem, ertapenem, amoxicillin/clavulanic acid and rifampicin (35mg/kg);

- To determine the pharmacokinetic-pharmacodynamic parameters of meropenem, ertapenem, amoxicillin/clavulanic acid, and rifampicin (35mg/kg);

- To explore the validity of integrating a novel set of surrogate markers of efficacy;

- To determine the minimum inhibitory concentrations of study drugs, alone and in combination, for each participant's *Mycobacterium tuberculosis* isolate

4 Trial Design

4.1 Summary of Trial Design

This will be a phase 2 single-centre, open-labelled bactericidal activity study of intravenous meropenem administered twice and once daily, intravenous/intramuscular ertapenem administered once daily, rifampicin (35mg/kg) administered once daily, all in combination with oral amoxicillin/clavulanic acid, as well as oral amoxicillin/clavulanic acid alone, over 14 days in treatment-naïve, smear positive participants with drug-sensitive pulmonary TB. The study will first enrol two arms with once- daily treatment options along with half of the control arm, and will continue uninterrupted with the remaining arms and the second half of the control arm. This is done to have the results of the treatments that are most likely useful for selected patients in the clinic as soon as possible.

The study will enrol 113 participants: 15 participants, which is the standard group size for an exploratory EBA study, will be enrolled in each of 7 experimental treatment arms and 8 participants will be randomized to receive a control regimen of standard first line TB treatment as per the South African TB guidelines (Rifafour® e-275). The study will be randomized, but not blinded. The study endpoints are laboratory based and it will be ensured that all microbiology staff is blinded to treatment allocation. Subjects will undergo screening procedures within 7 days prior to hospitalization, will be admitted to the trial ward on day -2, or from screening if in the interest of the participant as per the investigator's decision and remain in hospital until 1 day after the last dose of investigational drug was given. In the case that for logistical reasons the FDG-PET/CT cannot be done on day 14 or 15 as per the allowed window, the FDG-PET/CT can be done on days 15, 16 or 17. In this setting the IP will be extended until the FDG-PET/CT has been done. Before discharge a full course of standard antituberculosis treatment will be initiated.

The 14 day duration of the dosing in this study is generally accepted as the longest time period that a new drug or regimen may be used in participants with TB as monotherapy.

4.2 Treatment Arms

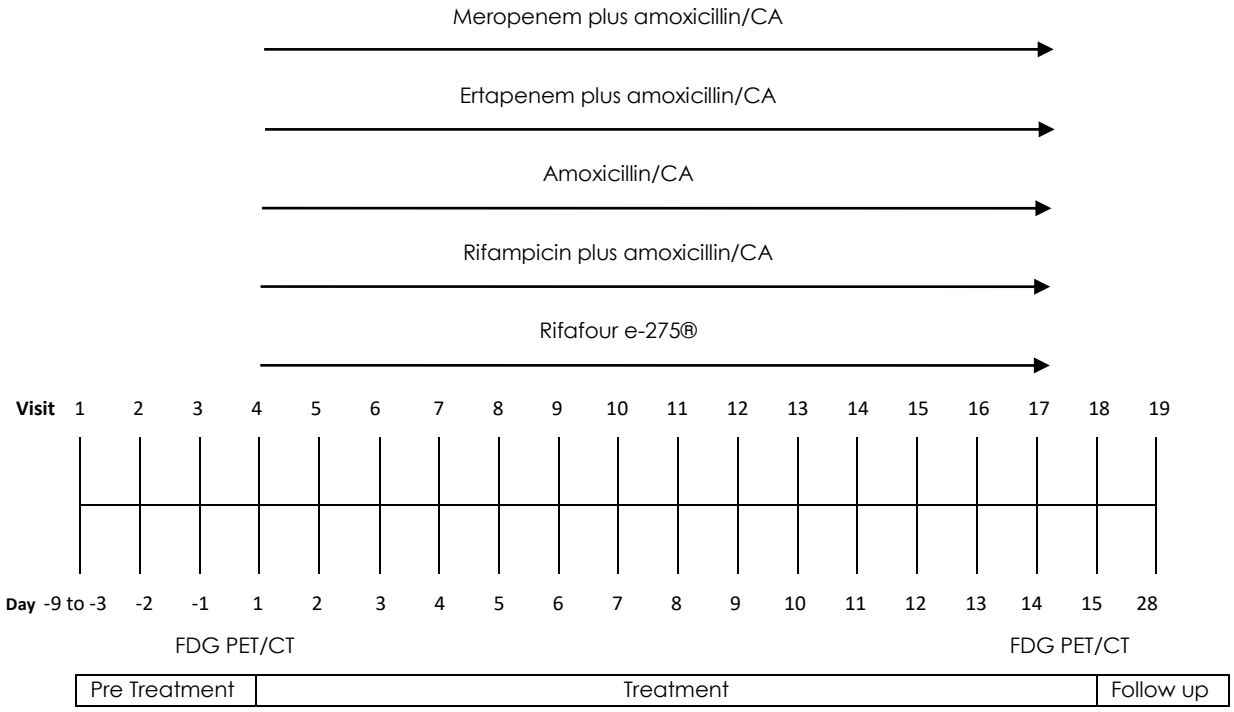
The groups will consist of 15 participants per treatment arm with a control arm of 4 participants in each group (Table 4).

Treatment Group	Treatment arm	Number per arm	Regimen components	
1	1	15	Meropenem IV 6 grams once daily infused over 6 hours	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	2	15	Ertapenem IM 1 gram once daily	Amx/CA oral 1000/62.5mg 2 tablets twice daily
Control		4	Rifafour (HRZE) Standard dose	-
2	3	15	Meropenem IV 3 gram twice daily each dose infused over 60 minutes	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	4	15	Ertapenem IV 1 gram once daily infused over 60 minutes	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	5	15	-	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	6	15	Rifampicin oral 35mg/kg once daily	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	7	15	Meropenem IV 4 grams OR 6 grams once daily infused over 60 minutes	Amx/CA oral 1000/62.5mg 2 tablets once daily
Control		4	Rifafour (HRZE) Standard dose	-

Table 4: Treatment Groups

In each treatment group standard HRZE treatment is included as a control for the EBA quantitative mycobacteriology and to evaluate whether HRZE in this population gives similar EBA results to that demonstrated in prior studies with this combination.

Figure 5: Trial Schematic



4.3 Trial Endpoints

4.3.1 Primary Endpoints

The EBA_{CFU}(0-14) as determined by the rate of change in logCFU per ml sputum over the period Day 0 to Day 14 which will be summarised and described with a statistical model as an estimated average decrease per day for patients in each group.

The EBA_{TTP}(0-14) as determined by the percentage rate of change in TTP per ml sputum over the period Day 0 to Day 14, which will be summarised and described with a statistical model as an estimated average increase per day for patients in each group.

P-values for the statistical significance of the estimated rates of change (slopes of fitted lines), as well as p-values for pair wise differences in rates of change between treatment groups will be given and graphically illustrated.

4.3.2 Secondary Endpoints

4.3.2.1 Activity

Drug activity with CFU or TTP over different treatment periods such as 0-2 days, 0-7 days, and 2-14 days as indicated, for cross-comparison with other published data.

Data will be displayed graphically, together with modelled estimates.

4.3.2.2 Safety and Tolerability

Incidence of treatment emergent adverse events (TEAEs) will be summarised by severity, IP relatedness, and seriousness, leading to early withdrawal and leading to death. Information on all adverse events will be collected, but only grade 2 or higher events and those of practical relevance i.e. diarrhoea and events related to injections, will be captured in the CRF.

4.3.2.3 Pharmacokinetics (PK)

The maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), the minimum observed plasma concentration (C_{min}) 24 hours following intake of the first daily dosing on day 14, area under the plasma concentration time (t) curve from zero to 24 hours (AUC(0-24)) will be estimated for all analytes in all treatment arms.

4.3.2.4 Pharmacokinetics-Pharmacodynamics (PK-PD)

The EBA_{CFU}(0-14), EBA_{CFU}(0-2), and EBA_{CFU}(2-14) versus the following PK variables will be graphically presented for meropenem, ertapenem, amoxycillin/clavulanic acid and rifampicin (35mg/kg):

- Cmax;
- AUC(0-24);
- Time over minimum inhibitory concentration (TMIC) for meropenem, ertapenem, amoxicillin/clavulanic acid, and rifampicin (35mg/kg)

4.3.2.5 Biomarkers

An exploratory component consisting of novel clinical parameters such as positron emission tomography (PET) scanning and biomarker sample collection (e.g. blood and urine) for a variety of immunological response biomarkers, at specified time points.

4.3.2.6 Mycobacteriology Characterization

1. The identifying organism will be confirmed as *Mycobacterium tuberculosis* at least once by polymerase chain reaction (PCR) either at screening (GeneXpert or Line Probe) and on a culture grown from a sample collected before treatment
2. Drug susceptibility testing of *Mycobacterium tuberculosis* for sensitivity to rifampicin with a molecular method will be tested at the screening visit (GeneXpert). Susceptibility to INH and RIF will be confirmed on a culture grown from a sample collected before treatment either by phenotypical testing or line probe.
3. A culture will be grown from a sputum sample submitted before treatment initiation (baseline) for confirming that the infecting organism is *M. tuberculosis* susceptible to isoniazid and rifampicin (GenoType MTBDRplus, Hain, Nehren, Germany). Cultures from baseline and from day 14 sputum will be kept for determination of the minimum inhibitory concentration (MIC) of the investigational agents that the subject was treated with. If a Day 14 culture is not available the last available culture after Day 8 will be kept. MIC tests for beta-lactams are under development and cultures might be exported for this purpose.

4.4 Trial Population

4.4.1 Inclusion Criteria

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

1. Provide written, informed consent prior to all trial-related procedures including HIV testing.
2. Male or female, aged between 18 and 65 years, inclusive.
3. Body weight (in light clothing and with no shoes) between 40 and 90 kg, inclusive.
4. Newly diagnosed, previously untreated, rifampicin-susceptible pulmonary TB.
5. A chest X-ray picture which in the opinion of the Investigator is consistent with TB.
6. Sputum positive on direct microscopy for acid-fast bacilli on at least one sputum sample (at least 1+ on the IUATLD/WHO scale).
7. Ability to produce an adequate volume of sputum as estimated from an overnight sputum collection sample (estimated 10 ml or more).
8. Be of non-childbearing potential or using effective methods of birth control, as defined below:
   Non-childbearing potential:

(a) Participant - not heterosexually active or practicing sexual abstinence; or
(b) Female participant/sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or
(c) Male participant/sexual partner - vasectomised or has had a bilateral orchidectomy minimally three month prior to screening;
Effective birth control methods:
(a) Double barrier method which can include a male condom, diaphragm, cervical cap, or female condom (male and female condoms should not be used together); or
(b) Barrier method combined with hormone-based contraceptives or an intra-uterine device for the female partner; and are willing to continue practicing birth control methods throughout participation in the study until Visit 19 (day 28).
(Note: hormone-based contraception alone may not be reliable when taking IP; therefore, hormone-based contraceptives alone cannot be used by female participants to prevent pregnancy).

4.4.2 Exclusion Criteria

Participants will be excluded from participation if they meet any of the following criteria.

1. Evidence of clinically significant conditions or findings, other than the indication being studied, particularly epilepsy, that might compromise safety or the interpretation of trial endpoints, per discretion of the Investigator.
2. Poor general condition where any delay in treatment cannot be tolerated per discretion of the Investigator.
3. A history of TB less than 3 years ago.
4. Clinically significant evidence of extrathoracic TB (miliary TB, abdominal TB, urogenital TB, osteoarthritic TB, TB meningitis), as judged by the Investigator.
5. History of allergy to any of the trial IP/s or related substances i.e. β-lactams and penicillin, as confirmed by the clinical judgement of the Investigator.
6. Known or suspected, current or history of within the past 2 years, alcohol or drug abuse, that is, in the opinion of the Investigator, sufficient to compromise the safety or cooperation of the participant.
7. HIV infected participants.
8. Having participated in other clinical studies with investigational agents within 8 weeks prior to trial start.
9. Female participant who is pregnant, breast-feeding, or planning to conceive a child within the anticipated period of participating in the trial. Male participant planning to conceive a child within the anticipated period of participating in the trial.
10. Subjects with diabetes (Type 1 or 2), point of care HbA1c above 6.5, or random glucose over 11.1 mmol/L.
11. Hypersensitivity to local anaesthesia of amide type.
12. Treatment received with any drug active against *MTB* (including but not limited to isoniazid, ethambutol, amikacin, cycloserine, fluoroquinolones, rifabutin, rifampicin, streptomycin, kanamycin, para-aminosalicylic acid, rifapentine, pyrazinamide, thioacetazone, capreomycin, thioamides, metronidazole), or with immunosuppressive medications such as TNF-alpha inhibitors or systemic or inhaled corticosteroids, within 2 weeks prior to screening
13. Participants with the following toxicities at screening as defined by the enhanced CTCEA toxicity table
    a. creatinine grade 2 or greater (>1.5 times upper limit of normal [ULN]);
    b. haemoglobin <7.5 g/dL;
    c. platelets grade 2 or greater (under $50x10^9$ cells/L);
    d. serum potassium grade 2 or greater (<3.0 mEq/L);
    e. aspartate aminotransferase (AST) grade 3 (≥3.0 x ULN) to be excluded;
    f. alanine aminotransferase (ALT) grade 3 (≥3.0 x ULN) to be excluded;
    g. APTT grade 3
    h. INR grade 3

i. Total white cell count grade 3

4.5 Restrictions

4.5.1 Foods and Beverages

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Methyl-xanthines/caffeine, poppy seeds, alcohol and grapefruit or grapefruit juice from Visit 1 (days -9 to -3) until after Visit 18 (day 15) or early withdrawal visit i.e. until discharge from the study clinic. Decaffeinated drinks are allowed.

4.5.2 Prior and Concomitant Medications

Any medication taken within 30 days prior to IP administration or during the trial until visit 19 (day 28) is defined as concomitant medication and is to be reported on the concomitant medication page of the case report form (CRF). Reported information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication. Any changes in the dosage of concomitant medication must also be reported on the concomitant medication page of the CRF. Data on concomitant medication will be collected up to the follow-up visit, even after early withdrawal of a participant.

Concomitant treatments should be kept to a minimum during the trial. However, if concomitant treatments are considered to be necessary for the participant's welfare and are unlikely to interfere with the investigational product, they may be given at the discretion of the Investigator. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition occurring after signing of the Informed Consent Form (ICF), the condition must be documented on the concomitant pages of the CRF.

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 medications are prohibited during administration of IP and up to the follow-up visit:

- Probenecid
- Sodium valproate
- Furosemide
- Diuretics that deplete potassium;
- Medicinal products used to treat pulmonary TB: flouroquinolones (including moxifloxacin, gatifloxacin and levofloxacin), isoniazid, ethambutol, amikacin, cycloserine, rifabutin, rifampicin, streptomycin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides and metronidazole.

4.5.3 Activity

Participants will be requested not to undertake vigorous exercise during the period from Visit 1 (days -9 to -3) until after the follow up Visit 19 (day 28).

4.6 Treatment Discontinuation and Participant Withdrawal

A participant must immediately discontinue treatment and be prematurely withdrawn from the trial for the following reasons:

- withdrawal of informed consent;
- Investigator considers it for safety reasons in the best interest of the participant that he/she be withdrawn;
- specific Toxicities as described in section 7.3;
- serious adverse event (SAE) if in the opinion of the investigator;
- pregnancy;
- at the specific request of the Sponsor or termination of the study by the Sponsor.

A participant who, in the opinion of the Investigator or Sponsor, fails to comply with the protocol will be withdrawn. Participants who withdraw from the study before they have received all 14 days' of IP, will be replaced.

All participants withdrawn/treatment discontinued will be referred to the local community TB clinics for standard anti-tuberculosis chemotherapy according to national guidelines. The participants will be provided with a referral letter to take with them to the TB clinic. Participants will be provided with sufficient TB medication to cover the time period from attending their last visit at the study clinic until their scheduled visit at the TB clinic.

4.7 Treatment Plan: Schedule of Assessments

The trial consists of three periods, as follows:

- Pre-Treatment Period (Visit 1/Day -9 to -3 to Visit 3/Day -1);
- Treatment Period (Visit 4/Day 1 to Visit 18/Day 15);
- Follow-Up Period (Visit 19/Day 28).

Refer to:

- Study Flow Chart (section 1) for the timing of all procedures and laboratory samples to done at each visit;
- Trial Procedures (section 6) for details regarding specific procedures or laboratory tests.

4.7.1 Pre-Treatment Period (Visit 1/Days -9 to -3 to Visit 3/Day -1)

4.7.1.1 Visit 1/Day -9 to -3

Prior to Visit 1, participants must have a positive GeneXpert 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;
- Demographic data;
- Clinically significant medical and treatment history;
- Eligibility assessment;
- Chest X-ray;
- Physical examination including height;
- Vital signs including weight;
- 12-lead ECG;
- Spot sputum (rifampicin resistance rapid test, confirmation of *MTB,* bacterial load, adequate sputum production);
- Haematology, clotting, clinical chemistry, urinalysis laboratory tests;
- Urine drug screen (should be repeated at Visit 2 (day -2) if participant not hospitalized at Visit 1 (day -9 to -3));
- Serum pregnancy test (women of child bearing potential only, whether they are sexually active or not);
- HIV test;
- Hospital admission (participants may be hospitalized during the entire pre-treatment period if the Investigator considers it advisable);
- Overnight sputum collection;
- Randomization by the pharmacist/registered dispenser may occur once all the screening results are available and the Investigator has determined that the participant is eligible for the trial.

Participants may proceed with the Visit 2 (day -2) assessments as soon as their Visit 1 (days -9 to -3) assessments have been completed. Visits 1 and 2 may occur on the same day if the screening results are available in time for randomization. Overnight sputum collection may be collected for a number of more days during the pre-treatment period if the screening results are delayed, or the mycobacterial testing on the first spot sputum shows an indeterminate or unfavourable results in which

case the test may be repeated on a freshly collected spot sputum or an overnight sputum and that result used. Of the pre-treatment period samples collected only the Visit 2 (day-2) and Visit 3 (day -1) overnight sputum samples will be used for the activity endpoint tests.

4.7.1.2 Visit 2/Day -2

The following information will be collected and procedures performed:

- Vital signs including weight;
- Point of care blood glucose (to coincide with the PET scan);
- Urine pregnancy test (to coincide with the PET scan);
- Hospital admission (Participants to be hospitalized on visit 2 if not hospitalised at visit 1);
- Overnight sputum collection (activity variable tests and mycobacterial characterization testing);
- Concomitant medication/s;
- Urine drug screen (urine drug screen can be repeated at Visit 2 (day -2) for participants who were not hospitalized at Visit 1 (day -9 to -3).
- FDG-PET/CT (if not to be done at visit 3)
- Randomization by the pharmacist/registered dispenser may occur once all the screening results are available and the Investigator has determined that the participant is eligible for the trial;

4.7.1.3 Visit 3/Day -1

The following information will be collected and procedures performed:

- Eligibility assessment;
- Vital signs including weight;
- Point of care blood glucose (to coincide with the PET scan);
- Urine pregnancy test (to coincide with the PET scan);
- Overnight sputum (activity variable tests);
- Randomization by the pharmacist/registered dispenser may occur once all the screening results are available and the Investigator has determined that the participant is eligible for the trial;
- Concomitant medication/s.
- FDG-PET/CT (if not done at visit 2)

4.7.2 Treatment Period (Visit 4/Day 1 to Visit 18/Day 15)

4.7.2.1 Visit 4/Day 1

The following information will be collected and procedures performed:

- Symptom-directed physical examination, as required;
- Vital signs including weight;
- Haematology, clinical chemistry, urinalysis laboratory tests;
- Urine and blood biomarkers;
- Overnight sputum (activity variable tests);
- IP administration and compliance check ('hand-and-mouth');
- Concomitant medication/s;
- Adverse events.

4.7.2.2 Visits 5 to 16 (days 2 to 13)

The following information will be collected and procedures performed:

- Daily:
    - Symptom-directed physical examination, as required;
    - Vital signs including weight;
    - Overnight sputum (activity variable tests);
    - IP administration and Compliance check ('hand-and-mouth');
    - Concomitant medication/s;
    - Adverse events.

- Visit 6 (day 3)
    - Urine and blood for biomarkers

- Visit 10 (day 7)
    - Urine and blood for biomarkers

- Visit 11 (day 8)
    - Haematology, clinical chemistry, urinalysis laboratory tests;

4.7.2.3 Visit 17/Day 14

The following information will be collected and procedures performed:

- Symptom-directed physical examination;
- Vital signs including weight;
- Haematology, clinical chemistry, urinalysis laboratory tests;
- PK sampling: to be performed at hours 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 in relationship to the time of dosing of the first daily dosing (24 hour post dose PK to be done on day 15);
- Urine and blood biomarkers;
- Point of care blood glucose (to coincide with the PET scan);
- Urine pregnancy test (to coincide with the PET scan);
- Overnight sputum (activity variable tests);
- IP administration and compliance check ('hand-and-mouth');
- Concomitant medication/s;
- Adverse events.
- FDG-PET/CT (if not done at visit 17, to be done within 3 days after visit 17)

4.7.2.4 Visit 18/Day 15

The following information will be collected and procedures performed:

- Symptom-directed physical examination, as required;
- Vital signs including weight;
- PK sampling: to be performed at 24 hours after time of first dosing on day 14;
- Point of care blood glucose (to coincide with the PET scan);
- Urine pregnancy test (to coincide with the PET scan);
- Overnight sputum (completion of day 14 collection)(activity variable tests);
- Concomitant medication/s;
- Adverse events;
- Discharge from hospital with referral letter to National TB treatment programme. The participants on the IP arms will receive their first dose/s of standard TB therapy per SA national TB treatment guidelines. The participants in the group receiving standard TB treatment will receive an additional dose/s to continue on this treatment. All participants will be referred to the local community TB clinics for a full course of standard antituberculosis chemotherapy according to national guidelines. The participants will be provided with a referral letter to take with them to the TB clinic. Within a week of the participant's discharge from the study clinic, a follow-up call will be made by the study site staff to the TB clinic to determine if the participant attended the clinic. Participants will be provided with sufficient TB medication (Rifafour e-275®) to cover the period from attending their last visit at the study clinic until their scheduled visit at the TB clinic.

4.7.2.5 Early Withdrawal

In case of early withdrawal during the treatment period of the study, 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:

- Symptom-directed physical examination;
- Vital signs including weight;
- Haematology, clinical chemistry, urinalysis laboratory tests;
- Urine and blood biomarkers;
- Serum pregnancy test;
- PK sampling;

- Concomitant medication/s;
- Adverse events;
- Discharge from hospital with referral letter to National TB treatment programme. The participants on the IP arms will receive their first dose/s of standard TB therapy per SA national TB treatment guidelines. The participants in the group receiving standard TB treatment will receive an additional dose/s to continue on this treatment. All participants will be referred to the local community TB clinics for a full course of standard antituberculosis chemotherapy according to national guidelines. The participants will be provided with a referral letter to take with them to the TB clinic. Within a week from the participant's discharge from the study clinic, a follow-up call will be made by the study site staff to the TB clinic to determine if the participant attended the clinic. Participants will be provided with sufficient TB medication (Rifafour e-275®) to cover the period from attending their last visit at the study clinic until their scheduled visit at the TB clinic.

All participants who received at least one dose of IP will be requested to return for the safety follow up visit, Visit 19 (in the case of and early withdrawal, 14 days ± 2 days after their early withdrawal visit).

4.7.3 Follow-Up Period (Visit 19/Day 28 ± 3 days)

4.7.3.1 Visit 19/Day 28 ± 3 days

The following information will be collected and procedures performed:

- Physical examination;
- Vital signs including weight;
- Haematology, clinical chemistry, urinalysis laboratory tests;
- Single 12-lead ECG;
- Concomitant medication/s;
- Adverse events.

4.8 Stopping Rules

There are no trial specific stopping rules.

The Sponsor has the right to stop the trial or the investigational site at any time, although this should only occur after consultation between involved parties. Should this occur the local 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 destructed as per the site's SOP, as instructed by the Sponsor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Participants currently on treatment will receive an appropriate regimen and all participants will be referred as soon as possible to the national TB programme.
Criteria for discontinuing IP administration for individual participants are noted in Section 7.3, Monitoring and Safety for Specific Toxicities.

4.9 Participant Progress Definitions

- **Screening Failure**

Participants from whom informed consent is obtained and is documented in writing (that is, participant signs an informed consent form), but who's not randomized due to him/her not meeting eligibility criteria.

- **Completed Treatment**

Participants who complete their 14 day treatment.

- **Early Withdrawal**

Participants who withdraw/are withdrawn from the study after signing the informed consent but prior to the completion of their 14 day treatment.

- **Completed Trial**

Participants who complete the last visit (Visit 19/day 28) of the trial.

- **Lost to Follow-up**

Participants who cannot be contacted up to a month (30 days) after the last visit date (Visit 19/day 28) of the trial. All attempts to contact the participant must be documented.

5 Investigational Product (IP)

5.1 Trial Treatments

IP to be used in this study include meropenem, ertapenem, rifampicin, amoxicillin/CA and an approved combination treatment for drug-sensitive TB (Rifafour®e275). Rifampicin and amoxicillin/CA will be given orally. Meropenem will be given intravenously, while ertapenem will be administered intravenously and intramuscularly. Rifafour®e275 will be given orally as tablets with dose based on weight according to local TB control program recommendations.

Drug procurement: investigational products will be sourced locally by the clinical trial site.

Treatment will be administered to the participants for 14 consecutive days. They will be randomized to one of the treatment arms in group 1 and once group one plus the 4 control participants has been enrolled, randomization into group 2 will start. Treatment groups are summarized in table 5 below.

Treatment Group	Treatment arm	Number per arm	Regimen components	
1	1	15	Meropenem IV 6 grams once daily infused over 6 hours	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	2	15	Ertapenem IM 1 gram once daily	Amx/CA oral 1000/62.5mg 2 tablets twice daily
Control		4	Rifafour (HRZE) Standard dose	-
2	3	15	Meropenem IV 3 gram twice daily each dose infused over 1 hour	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	4	15	Ertapenem IV 1 gram once daily Infused over 1 hour	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	5	15	-	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	6	15	Rifampicin oral 35mg/kg once daily	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	7	15	Meropenem IV 6 grams OR 4 grams once daily infused over 1 hour	Amx/CA oral 1000/62.5mg 2 tablets once daily
Control		4	Rifafour (HRZE) Standard dose	-

Table 5: Treatment Groups

5.2 Method of Assigning Participants to Treatment Groups

Eligible participants who have given written, informed consent will be enrolled onto the trial during Visit 1 (days -9 to -3) and will be identified by a study generated participant identification code for anonymity (participant number). Participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and assigned a treatment number.

The randomization scheme will be generated by the study statistician/data manager. Randomization will be done 1:1:1 in group 1 and the 4 controls first. Once all participants of group 1, as well as the 4 controls have been fully enrolled, randomization into group 2 and the 4 controls will be done 1:1:1:1:1. Consecutively numbered, sealed, opaque envelopes will be prepared and provided to the site. The site research pharmacist will maintain the randomization envelopes in a secured location. After being notified that a participant is eligible for the trial, the research pharmacist will write the participant's number on the next numbered envelope and open it to determine the participant's treatment group. The participant number, participant initials, the date and time the envelope was opened, and the signature of the person opening the envelope will be recorded on the treatment group card in the envelope at the time it is opened. Opened envelopes containing treatment group cards will then be filed in the participants' source file.

Participants withdrawn from the trial before they have received all 14 doses of IP, will be replaced.

Participants will be enrolled into the additional meropenem arm (group 2, arm 7) following completion of enrolment into arms 3 to 6. Within arm 7, participants will be randomized 1:1 to either receive 4 grams or 6 grams of meropenem administered as a 1 hour infusion.

5.3 IP Administration

5.3.1 Route and Dosage

Meropenem and Amoxicillin/CA Once Daily Treatment Arm 1

Meropenem will be administered as 6 grams once daily for 14 days, intravenously over 6 hours (+/- 10 minutes) in total. Two dilutions of 3 grams meropenem will be prepared and stored as described in section 5.3.3. Each of the 2 dilutions containing 3 grams of meropenem will be infused over 3 hours (+/- 5 min), with no more than 5 minutes lapsing while replacing the first dilution (bag) with the second dilution with meropenem 3 grams.

Amoxicillin/CA will be administered orally as Amx/CA 1000/62.5mg, 2 tablets twice daily for 14 days with 250ml of water each, 15 minutes (+/- 5 min) after the start of the infusion.

Meropenem and Amoxicillin/CA Twice Daily Treatment Arm 3

Meropenem will be administered as 3 grams twice daily for 14 days, intravenously by bolus infusion over 1 hour (+/- 10 minutes).

Amoxicillin/CA will be administered orally as Amx/CA 1000/62.5mg, 2 tablets twice daily for 14 days with 250ml of water each, 15 minutes (+/- 5 min) after the start of the infusions.

Ertapenem and Amoxicillin/CA Once Daily Intravenous Treatment Arm 4

Ertapenem will be administered as 1gram daily for 14 days, intravenously by bolus infusion over 1 hour (+/- 10 min).

Amoxicillin/CA will be administered orally as Amx/CA 1000/62.5mg, 2 tablets twice daily for 14 days with 250ml of water each, 15 minutes (+/- 5 min) after the start of the infusion.

Ertapenem and Amoxicillin/CA Once Daily Intramuscular Treatment Arm 2

Ertapenem will be administered as 1gram daily for 14 days, intramuscularly.

Amoxicillin/CA will be administered orally as Amx/CA 1000/62.5mg, 2 tablets twice daily for 14 days with 250ml of water each, 15 minutes (+/- 5 min) after the IM injection was given.

Rifampicin and Amoxicillin/CA Once Daily Treatment Arm 6

Rifampicin will be administered at a dose of 35mg/kg once daily for 14 days with a full glass of water (250ml) 1 hour (+/- 5 min) before the start, or 2 hours (+/- 5min) after the completion of a meal. The dosage of the Rifampicin will be rounded off to the closest available tablet size.

Amoxicillin/CA will be administered orally as Amx/CA 1000/62.5mg, 2 tablets twice daily for 14 days with 250ml of water each,15 minutes (+/- 5 min) after the IP was taken orally.

Amoxicillin/CA Twice Daily Treatment Arm 5
Amoxicillin/CA will be administered orally as Amx/CA 1000/62.5mg, 2 tablets twice daily for 14 days with 250ml of water each.

Meropenem and Amoxicillin/CA Once Daily Treatment Arm 7
Meropenem will be administered as 6 grams or 4 grams once daily for 14 days, intravenously over 1 hour (+10 minutes) in total. One dilution of either 6 grams or one dilution of 4 grams of meropenem will be prepared and stored as described in section 5.3.3. The dilution containing either 6 grams or 4 grams of meropenem will be infused over 1 hour.

Amoxicillin/CA will be administered orally as Amx/CA 1000/62.5mg, 2 tablets once daily for 14 days with 250ml of water each, 15 minutes (+/- 5 min) after the start of the infusion.

Rifafour e275® Treatment Arms
The Rifafour e-275® will be administered once daily for 14 days with a full glass of water (250ml) 1 hour before the start, or 2 hours after the completion of a meal (as per the package insert). Pyridoxine 25mg daily will be given to all participants receiving Rifafour e275®.

Rifafour e275® will be administered according to the South African National TB Treatment Guidelines. The daily dose is dependent on the participants' weight as follows: 40 - 54kg: 3 tablets; 55 – 70kg: 4 tablets; 71kg and over: 5 tablets.

5.3.2 Dosing Times
Dosing of the IP will be for 14 days. The first daily dose will be done between 06h00 and 11h00, at a specific time point as identified by the site. This first daily dosing time will remain the same for the 14 days.

Morning dosing time of the meropenem, ertapenem and rifampicin (treatment arms 1, 2, 3, 4, 6 and 7) will be recorded as the first dosing time of the day. The second dose's time, applicable for treatment arm 3, (12 hours later) will be calculated from the start time of the first dose of the day.

Dosing time of the first amoxicillin/CA (treatment arms 1, 2, 3, 4, 6 and 7) will be calculated from the dosing time of first morning dose and the second dose amoxicillin/CA dose will be calculated 12 hours from the first morning dose of amoxicillin/CA (applicable for treatment arms 1, 2, 3, 4, and 6).

For treatment arms 5, the first amoxicillin/CA will be dosed in the morning and the second dose will be 12 hours from the amoxicillin/CA first morning dose.

5.3.3 IP Reconstitution
Meropenem IV infusion will be provided in reconstitution vials containing 1g of meropenem each. Each vial will be reconstituted with 10ml sodium chloride 9 mg/mL (0.9 %) for IV administration. Constitute the vial with 10ml of sodium chloride 9 mg/mL (0.9 %), shake to dissolve and let stand until clear. An approximate volume of 10ml will be withdrawn from each of the vials into a syringe.

For the 3 gram twice daily treatment arm, the contents of 3 x 1g reconstituted vials should be added to 50 ml of sodium chloride 9 mg/mL (0.9 %). This should be an approximate average concentration of 40mg/ml.

For the 6 gram daily treatment arm 1, 2 dilutions containing 3 gram meropenem each, will be prepared. The contents of 3 x 1 gram reconstituted vials should be added to 50ml of sodium chloride 9 mg/mL (0.9 %) (diluted). This dilution will be an approximate average concentration of 40mg/ml.

For the 6 gram daily treatment arm 7, 1 dilution containing 6 gram meropenem, will be prepared. The contents of 6 x 1 gram reconstituted vials should be added to 40ml of sodium chloride 9 mg/mL (0.9 %) (diluted).

For the 4 gram daily treatment arm 7, 1 dilution containing 4 gram meropenem, will be prepared. The contents of 4 x 1 gram reconstituted vials should be added to 60ml of sodium chloride 9 mg/mL (0.9 %) (diluted).

The dilution may be stored for up to 4 hours at room temperature (15º – 25º C) or for up to 24 hours between 2º – 8ºC. If stored between 2º – 8ºC, the dilution must reach room temperature (taken out of the fridge between 30 minutes and 1 hour before administration) before IV administration and should be administered within 4 hours after taken from the fridge. Care will be taken not to freeze solutions of meropenem. The IV line should be flushed with at least 5 ml of sterile water for injection after completion of the administration of the meropenem.

Ertapenem IV will be supplied in packs of 1 or 10 vials, with each vial containing 1 gram of ertapenem. The contents of a 1 g vial of ertapenem will be reconstituted with 10 mL of water for injection or sodium chloride 9 mg/mL (0.9 %) solution to yield a reconstituted solution of approximately 100 mg/ml. It will be shaken well to dissolve. For IV administration, reconstituted ertapenem must be diluted immediately. We will add reconstituted 1g ertapenem to 50 mL of sodium chloride 9 mg/mL (0.9 %) solution. Diluted solutions for intravenous use are physically and chemically stable for 6 hours at room temperature (15 - 25°C) or for 24 hours between 2ºC to 8°C, after time of reconstitution. If stored between 2º – 8ºC, the diluted ertapenem must reach room temperature (taken out of the fridge between 30 minutes and 1 hour before administration) before IV administration. Dilutions should be used within 4 hours of their removal from the refrigerator. Care will be taken not to freeze solutions of ertapenem. The IV line should be flushed with at least 5 ml of sterile water for injection after completion of the administration of the ertapenem.

Ertapenem IM will be supplied in packs of 1 or 10 vials, with each vial containing 1 gram of ertapenem. Reconstitute the contents of a 1 g vial of ertapenem with 3.2 mL of 1.0% lidocaine HCl injection (without adrenalin). Shake vial thoroughly to form solution. Withdraw the contents of the vial and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh). The reconstituted IM solution should be used within 1 hour after preparation. The reconstituted IM solution should not be administered intravenously.

5.3.4 Participant Compliance

The IP will be administered by the investigator/designated site personnel. The date, time, number of tablets or dosage of intravenous and intramuscular IP, will be recorded in the participant's CRF and in the source documents. All oral IP will be administered with water. Participants will be checked for IP compliance by the Investigators or trial personnel via the hand-and-mouth procedure. Both the hand and mouth of the participant will be checked to ensure that the participant has swallowed the IP. All syringes and vials will be checked to ensure complete administration.

5.4 Blinding and Procedures for Breaking the Blind

This is an open label study and there is therefore no need for blinding or procedures to break the blind. However the mycobacteriology laboratory will remain blinded until closure of the EBA results.
The complete formulations of the meropenem, ertapenem, amoxicillin/CA, rifampicin and Rifafour e275® are found in the applicable Package Inserts.

5.5 Packaging

Trial medication will be supplied as follows:

Rifafour e275®, meropenem, ertapenem, rifampicin and amoxicillin/CA will be sourced locally and labelled appropriately. Oral IP will be stored and dispensed into labelled containers to each participant at randomisation. Intravenous and intramuscular IP will be prepared as per the instructions provided in the registered package inserts.

Participants will receive the following trial medication, depending on which group they are randomized to (Table 6).

Treatment Group	Treatment arm	Number per arm	Regimen components	
1	1	15	Meropenem IV 6 grams once daily infused over 6 hours	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	2	15	Ertapenem IM 1 gram once daily	Amx/CA oral 1000/62.5mg 2 tablets twice daily
Control		4	Rifafour (HRZE) Standard dose	-
2	3	15	Meropenem IV 3 gram twice daily each dose infused over 1 hour	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	4	15	Ertapenem IV 1 gram once daily infused over 1 hour	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	5	15	-	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	6	15	Rifampicin oral 35mg/kg once daily	Amx/CA oral 1000/62.5mg 2 tablets twice daily
	7	15	Meropenem IV 6 grams OR 4 grams once daily infused over 1 hour	Amx/CA oral 1000/62.5mg 2 tablets once daily
Control		4	Rifafour (HRZE) Standard dose	-

Table 6: Investigational Medicinal Product Details

5.6 Labelling

The meropenem, ertapenem, rifampicin, amoxicillin/CA and Rifafour e-275®, will be sourced locally.

After dispensing the daily containers/vials of each treatment, the outer container will be labelled with, at a minimum, the following information:

- Protocol number and name of Sponsor;
- Name of medication;
- Dosage, quantity and method of administration;
- Batch number;
- Investigational product name;
- Directions for use;
- Storage conditions;
- The statement "For Clinical Trial Use Only";
- Name of Investigator and site details;
- Participant details.

5.7 Storage

All investigational products will be kept securely stored by the site pharmacist/registered dispenser in a secured area with limited access to designated site personnel only. Only qualified personnel will undertake the preparation, handling and safe disposal of investigational products. Logs will be kept for drug accountability (chain of custody) and temperature.

Meropenem (powder form) will be stored in the original packaging (thereby protected from light and moisture), between 15 to 25ºC. Once diluted it can be stored up to 4 hours at room temperature (15º

– 25ºC) or for up to 24 hours between 2º – 8ºC. Solutions of intravenous meropenem IV should not be frozen.

Ertapenem will be stored in the original packaging (thereby protected from light and moisture) below 25ºC . Diluted solutions for intravenous use are physically and chemically stable for 6 hours at room temperature (15ºC - 25°C) or for 24 hours between 2 - 8°C. Solutions should be used within 4 hours of their removal from the refrigerator. Do not freeze solutions of ertapenem. The reconstituted solution for intramuscular use, should be used within 1 hour after preparation.

Amoxicillin/CA should be stored at a temperature below 25ºC, protected from moisture and light.

Rifampicin should be stored below 25 °C and protected from light and moisture.

Rifafour e-275® will be stored between 15 - 25ºC, 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 IP. Accurate accountability records will be kept by the site to assure that the IP will not be dispensed to any person who is not a participant under the terms and conditions set forth in this protocol i.e. delivery to site, inventory at site, use by participant, 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 IP will be destructed by the site according to their standard operational procedure, or returned to the consortium partners (or designated contractor) and destructed according to their standard operational procedure. 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;
- Demographic data: date of birth, race, gender;
- Clinically significant medical and treatment history;
- Eligibility criteria;
- Chest X-ray: A PA-CXR will be taken according to local SOP. Abnormalities which will be considered to parallel a diagnosis of active tuberculosis, according to CDC criteria from the Tuberculosis component of Technical Instructions for the medical examination of Aliens in the USA May 2008 [76], are outlined below:
    1) Infiltrate or consolidation–Opacification of airspaces within the lung parenchyma. Dense or patchy with irregular, ill-defined, or hazy borders.
    2) Any cavitary lesion.
    3) Nodule with poorly defined margins–Round opacity within the lung parenchyma, with margins that are indistinct or poorly defined.
    4) Pleural effusion–Presence of a significant amount of fluid within the pleural space.
    5) Hilar or mediastinal lymphadenopathy–Enlargement of lymph nodes in one or both hila and/or within the mediastinum.
    6) Miliary Tuberculosis–nodules that are uniform in size, measuring 1 to 2 mm (millet size), distributed throughout the parenchyma.

- 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:
    - Urine:
        - Urine drug screen.
    - Serum:
        - βHCG pregnancy test: women of child-bearing potential only, whether they are sexually active or not.
    - Serology:
        - HIV

          Approval for this to be performed will be obtained from participants during the written informed consent process. Prior to HIV testing and on receipt of the results, participants will be counselled on HIV by the PI, Sub-Investigator or trained counsellors.
    - Spot sputum:
        - Rapid test for rifampicin resistance;
        - Confirmation of *MTB* prior to randomization;
        - Adequate bacterial load;
        - Estimate of adequate sputum production.
- Concomitant medications;
- Height (meters (m));
- Method of birth control: male and female participants;
- Restrictions: restricted food and beverages, restricted activity, prohibited medication;
- Post-trial treatment TB programme attendance: attendance at the local TB clinic, inclusion onto the national TB programme;
- Hospitalization.

6.2 FDG-PET/CT Scan

The FDG-PET/CT scan will be performed at a facility local to the study site in South Africa. Participants will consent to receive a maximum of 2 FDG-PET/CT scans during the study. The FDG-PET/CT scans will be performed on a Philips Gemini TF Big Bore or similar scanner (preferably the same scanner will be used for subjects receiving subsequent scans as was used on their first scan). Maximum effective dose associated with scans over a calendar year will be approximately 2.4 rem. Participants will be fully briefed with regard to what to expect and any precautions highlighted. Participants will be asked not to eat for approximately 6 hours prior to the scan but to drink plenty of water. Additional dietary regimens will be coordinated with dietary restrictions of the treatment so that no conflicting instructions exist on PET/CT days. Prior to the FDG-PET/CT scan, subjects will have point of care assessment of blood sugar. Following the blood test, a venous cannula will be inserted and 28 MBq/kg of radiolabeled ^{18}F-FDG, minimum total dose of 175 MBq and maximum of 260, administered. After about 50 minutes, subjects will void urine and at about 60 minutes after injection, the subjects will undergo a FDG-PET/CT scan of the chest (120 kV, 200 mA, 1 mm slice thickness). The subject will be oriented face up on the scanner bed with his or her hands above the head.

For clinical purposes, the scans will be reviewed by a trained radiologist. For research purposes, PET/CT scans will be scored by two or more independent observers blinded to the treatment arm. Our experience with over 100 scans indicates that observer concordance is excellent when consensus is first achieved on which lesions are simple vs. complex and which to include in the analysis. Simple lesions are composed of only a single lesion type whereas complex lesions are contiguous lesions composed of two or more lesion types. Based on this method, the readers will first agree by consensus on the PET/CT lesions to include in the analysis. The PET/CT scans will then be scored based on this consensus. Lesions will be stratified by simple vs. complex with measurements made of cavitary air volume (mL), hard lesion volume (Hounsfield unit -100 to 200; mL), soft lesion volume (Hounsfield unit -500 to -100; mL), and total glycolytic activity (TGA; total SUV*body weight). These measurements will be made at baseline and at two weeks to determine the resultant changes.

The PET/CT results can be made available, upon request, to the patient's physician(s) upon the patient's transfer to standard of care therapy.

6.3 Activity Variables and Procedures

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

- Overnight Sputum: the mycobacteriology sampling methodology and requirements will be described in a separate document, the laboratory manual, which will be provided prior to the trial start. The following analyses will be performed:
    - Number of CFU per ml sputum;
    - TTP.
- Using these observed variables the following derived variables will be assessed for evaluation of the activity endpoints:
    - The rate of change over timeframes in number of sputum CFU of MTB on solid media (change in logCFU per day);
    - The rate of change over timeframes in TTP in liquid media (the MGIT system) (change in TTP per day).

6.4 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:
    - Haematology: haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count;
    - Clinical chemistry: albumin, urea, creatinine, direct, indirect and total bilirubin, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactic dehydrogenase (LDH), sodium, potassium, calcium (corrected for albumin), chloride, random/fasting glucose;
    - Urinalysis: pH, specific gravity, protein, glucose, micro-albumin, ketones, bilirubin, creatinine, nitrite, sodium, urobilinogen, blood, leukocytes, microscopy;
- 12-lead electrocardiogram (ECG):
    - Investigator assessment: Normal, Abnormal;
    - Methodology:
        - Timing and registration technique for ECGs should be standardized for all participants (done according to the site SOP);
        - Participants 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;
- Physical Examination. Height is measured at screening only;
- Vital signs: supine systolic and diastolic blood pressure (SBP and DBP), heart rate, axillary/tympanic body temperature (it is preferable to choose one method throughout the study), weight. Using the observed variables weight and height;
- Adverse events;
- Concomitant Medication.

6.5 Pharmacokinetic Variables and Procedures

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

- Plasma concentrations. The PK laboratory sampling methodology and requirements will be described in a separate document, the laboratory manual, which will be provided prior to the trial start. Analyte/s measured are dependent on treatment arm (Table 7).

Treatment arm	Treatment	MIC
	Group 1	**Group 1**
1	Meropenem/ Amoxicillin/ CA	Meropenem/ Amoxicillin/ CA
2	Ertapenem/ Amoxicillin/ CA	Ertapenem/ Amoxicillin/ CA
	Group 2	**Group 2**
3	Meropenem/ Amoxicillin/ CA	Meropenem/ Amoxicillin/ CA
4	Ertapenem/ Amoxicillin/ CA	Ertapenem/ Amoxicillin/ CA
5	Amoxicillin/ CA	Amoxicillin/ CA
6	Rifampicin/ Amoxicillin/ CA	Rifampicin/ Amoxicillin/ CA
7	Meropenem/ Amoxicillin/ CA	Meropenem / Amoxicillin/ CA

Table 7: Analyte/s to be Measured per Treatment Arm

Using these observed variables the following derived variables will be measured/estimated for evaluation of the PK endpoints for Day 14:

- Maximum observed plasma concentration (C_{max});
- Time to reach Cmax (T_{max});
- Minimum observed plasma concentration (C_{min}) 24 hours following the last dose;
- Area under the plasma concentration time (t) curve from zero to 24 hours (AUC(0-24)).

No PK variables will be collected or derived on the Rifafour e275® treatment arm.

6.6 Biomarkers

Additional blood and urine samples will be collected at baseline (day 1), day 3, day 7, day 14 and early withdrawal. The sampling methodology and requirements will be described in a separate document, the Biomarker Manual, which will be provided prior to the trial start. The volumes of samples that will be collected at each time point are: urine approximately 50ml and blood up to 27ml. These samples will be stored at the clinic site from where it will be shipped for storage at a laboratory outside of South Africa. The samples will be stored for potential future analysis of biomarkers related to tuberculosis and its treatment and will not be used for human DNA genetic testing.

6.7 Mycobacteriology Characterization Variables and Procedures

The mycobacteriology characteristics of the Participants' MTB strains will be assessed at the time points described in the trial flow chart. The mycobacteriology 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 characteristics will be measured:

- GeneXpert at screening for presence of MTB and INH and Rif susceptibility
- MIC/s to be done on Visit 2 (day -2) or Visit 3 (day -2) and the last available culture if day 8 or later. MIC/s measured are dependent on treatment arm (Table 8).
- A culture will be grown from a sputum sample submitted before treatment initiation (baseline) for confirming that the infecting organism is *M. tuberculosis* susceptible to isoniazid and rifampicin (GenoType MTBDRplus, Hain, Nehren, Germany). Cultures from baseline and from day 14 sputum will be kept for determination of the minimum inhibitory concentration (MIC) of the investigational agents that the subject was treated with. If a Day 14 culture is not available the last available culture after Day 8 will be kept. MIC tests for beta-lactams are under development and cultures might be exported for this purpose.

7 Adverse Events

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

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation participant 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 participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- 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 whether an AE is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant 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 participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death had it been 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 9.

Table 9: 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 CTCAE Toxicity Table Version 4.04 dated 14 June 2010 (Appendix 1). For abnormalities **NOT found** elsewhere in the Toxicity Tables the scale described in Table 10 is to be used to estimate grade of severity:

Table 10: 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 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 IP

- IP unchanged;
- IP interrupted;
- IP stopped;
- Not applicable (Follow-up period).

Other Action Taken

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

Outcome

- Resolved;
- Improved;
- Unchanged;
- Worse;
- Fatal;
- Unknown.

Occurrence

- Once;
- Intermittent;
- Continuous.

7.2 Reporting

7.2.1 Adverse Event (AE)

Adverse events will be collected by the Investigator from the time a participant receives his/her first dose of study medication (visit 3) through to the day 28 Follow up Visit. Any clinically significant event noted between Visit 1 and Visit 4, will be recorded as medical history. Not clinically significant events will be noted in the source.

Any AE (serious or non-serious), grade 2 or higher, observed by the Investigator or reported by the participant 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 IP;
- Other action taken;
- Outcome;
- Relationship to IP;
- Occurrence;
- Seriousness.

7.2.2 Serious Adverse Events (SAE)

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

In addition, the Investigator will provide a detailed, signed, written, and complete SAE report form that addresses the Investigator's estimates of the attribution/causality of the AE to the IP 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 EC of all SAEs in accordance with local requirements and ICH guidelines for GCP.

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/referral clinic. However, this will have to be agreed upon with the Sponsor.

7.2.4 Post-Trial Adverse Events

Any new SAEs reported by the participant to the Investigator that occur up to 30 days after the last scheduled contact should be reported to the Sponsor on an expedited basis. Any additional new SAEs beyond this period that are determined by the Investigator to be possible, probable or very likely related to the use of the IP 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 participant. 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 participant, 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 participant while on the study will be assessed by the Investigator. If the symptom has:

- Worsened while the participant 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 participant's TB; and
- Not clinically significant;

It will not be recorded as an AE and this will be noted in the participant's source documentation.
All TB related symptoms that meet SAE criteria will be recorded and reported as a SAE.

7.2.7 Overdose

Overdose of IP experienced by the participant 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 participant's source documentation.

7.2.8 Drug Interaction

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

7.2.9 Pregnancy

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

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 that are 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, participants 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 (see package inserts).

7.3.1 Any other toxicities

Grade 1 or 2

Participants who develop grade 1 or 2 AE or laboratory toxicity may continue intake of IP.

Grade 3 or 4

Participants who develop grade 3 or 4 AE or laboratory toxicity (see Appendix 2 for specifics) will be carefully evaluated by the Investigator. Participants may continue intake of IP or be withdrawn from the trial if, in the opinion of the Investigator, the AE or laboratory toxicity poses a significant risk for the participant in case of continued participation in the trial. Participants should be followed as appropriate until resolution of the AE or toxicity.

8 Statistical Analysis

The statistical analysis plan (SAP), which will contain details of the analyses specified in this section, will be written and signed off prior to clinical database lock.

8.1 Analysis Population/s

All randomised participants who receive at least one dose of IP, will be included in the analyses.

8.2 Sample Size

The planned sample size of 15 participants per treatment group is in keeping with other phase 2 trials of this type and accounts for the possibility of up to 3 drop-outs per arm, which based on previous studies of this type conducted at these sites, represents a conservative estimate of the expected drop-out rate. Previous EBA studies indicate that the between participant standard deviation of logCFU can be approximately 0.2. Therefore, assuming similar variability in the new trial the expected standard errors of group mean EBA and corresponding width of 95% confidence intervals are described in the Table 11.

Table 11: Expected Standard Errors of Group mean log CFU and confidence intervals

Group Size	Standard Error	Width of 95%CI
15	0.052	0.101
10	0.063	0.124

8.3 Interim Analyses

When the first group (treatment arms 1 and 2) is completed, an interim analysis will be conducted without interrupting recruitment into group 2. Should the interim results indicate that one or both of these once-daily treatment options might be clinically useful we will disseminate these interim results. The final analysis will be done when all data is collected.

8.4 Endpoint Analysis

8.4.1 Primary Endpoint Analysis

The EBA_{CFU}(0-14) as determined by the rate of change in logCFU per ml sputum over the period day 0 to day 14 which will be described with at most 3 parameters from a linear, bi-linear or non-linear regression of logCFU on time.

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

8.4.2 Secondary Endpoint Analysis

8.4.2.1 Activity

- The EBA_{CFU}(0-2) and EBA_{CFU}(2-14) as determined by the rate of change of logCFU in sputum over the period day 0 to day 2 and day 2 to day 14, which will be described with at most 3 parameters from an appropriate function of logCFU on time.
- The EBA_{TTP}(0-2), EBA_{TTP}(0-14), and EBA_{TTP}(2-14) in the Mycobacterial Growth Indicator Tube (Bactec™ MGIT™ 960) system as determined by the rate of change in TTP in sputum over the periods day 0 to day 2, day 0 to day 14, and will be described with at most 3 parameters from an appropriate function of TTP on time.

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

8.4.2.2 Safety and Tolerability Analyses

- 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 IP and includes those events started prior to the first administration of IP but which worsened after the first intake. Adverse events starting after the last administration of IP 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 treatment-emergent adverse events (TEAEs);
    - Incidence of TEAEs by Severity;
    - Incidence of drug related TEAEs;
    - Incidence of Serious TEAEs;
    - Incidence of TEAEs leading to early withdrawal;
    - Incidence of TEAEs leading to death.
- Other safety variables: laboratory parameters, physical examination, vital signs, concomitant medication. Descriptive summary statistics will be presented.

8.4.2.3 Pharmacokinetic Analysis

The maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), the minimum observed plasma concentration (C_{min}) 24 hours following day 14, area under the plasma concentration time (t) curve from zero to 24 hours (AUC(0-24)) will be estimated for the following, on day 14:

Treatment Arm	**Analyte/s**
Meropenem plus amoxicillin/CA	Meropenem; amoxicillin; CA
Ertapenem plus amoxicillin/CA	Ertapenem; amoxicillin; CA
Rifampicin	Rifampicin; amoxicillin; CA
Amoxicillin/CA	Amoxicillin; CA
Rifafour e275®	None

No PK analyses will be performed on the Rifafour e275® treatment arm.
The following PK parameters will be estimated from participants' individual plasma concentrations (except in the Rifafour e275® treatment arm) by applying a noncompartmental approach using PK software such as WinNonlin Professional. Concentration values reported as below the limit of

quantitation will be set to zero. Each parameter will be calculated separately using plasma concentrations of meropenem and ertapenem and their respective metabolites, amoxicillin/CA and rifampicin. PK parameters will be estimated for day14 only.

- C_{max}: Maximum observed plasma drug concentration.
- T_{max}: Time at which C_{max} is observed (obtained without interpolation).
- C_{min}: Minimum observed plasma drug concentration 24 hours following the last dose.
- AUC(0-24): Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 24 hours.

Descriptive statistics including mean, standard deviation, coefficient of variation, median, minimum and maximum, geometric mean and geometric mean CV% will be computed for each PK parameter by group. Grouping will be by gender.
In addition, mean and median concentration-versus-time graphs will be provided (with error bars as appropriate).

8.4.2.4 Pharmacokinetic and Pharmacodynamic Analysis

The EBA_{CFU}(0-14), EBA_{CFU}(0-2), and EBA_{CFU}(2-14) vs. the following PK variables will be presented for Meropenem, ertapenem, amoxicillin/CA, and rifampicin:

- C_{max};
- AUC(0-24);
- Time over minimum inhibitory concentrations (TMIC).

These data will be presented as descriptive analyses, and no inferential tests will be carried out.
No PK-PD analyses will be performed on the Rifafour e275® treatment arm.

8.4.2.5 Mycobacteriology Characterization

Cultures grown from the overnight sputum collections from Baseline (day -2 or day -1) and the last available culture on a treatment day will be assessed as follows:

- A culture will be grown from a sputum sample submitted before treatment initiation (baseline) for confirming that the infecting organism is *M. tuberculosis* susceptible to isoniazid and rifampicin (GenoType MTBDRplus, Hain, Nehren, Germany). Cultures from baseline and from day 14 sputum will be kept for determination of the minimum inhibitory concentration (MIC) of the investigational agents that the subject was treated with. If a Day 14 culture is not available the last available culture after Day 8 will be kept. MIC tests for beta-lactams are under development and cultures might be exported for this purpose.

9 Records Management

9.1 Data Collection

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

9.2 Source Documents

Source documents are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments.
All source documents pertaining to this trial will be maintained by the Investigators. The Investigator has to permit trial related monitoring, audits, Independent Ethics Committee/Institutional Review Board (IEC/IRB) review and regulatory inspections providing authorized persons direct access to source documents.

9.3 File Management at the Trial Site

It is the responsibility of the Investigators to ensure that the trial site's files are maintained in accordance with South African Good Clinical Practice Guidelines and the ethical principles that have their origin in the Declaration of Helsinki.

9.4 Records Retention at the Trial Site

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.

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, South African GCP, and the ethical principles that have their origin in the Declaration of Helsinki.

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 bio analytical activities relevant to the quality of the study. Participant 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 Principal Investigator may appoint other Sub-Investigators to assist with the study. However the Principal 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 SA-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 trial site and must accept the various monitoring procedures employed by the Sponsor. The purpose of monitoring is to verify that the rights and well-being of human participants 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), participant 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 South African GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

11.2 Independent Ethics Committee Review

The protocol and required study related documents will be reviewed by the site's EC. The study will not start until the EC has approved the protocol, written informed consent, any written information to be provided to the participant or any modification thereof, plus any other study related documents required for review. The IEC/IRB shall be constituted and shall operate in accordance with South African GCP, 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 EC. 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 participants (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 participant 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 participant 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 EC 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 participant and fully explained by the Investigators (or qualified designees) and it is felt that the participant understands the

implications of participating, the EC approved written informed consent form will be signed and dated by both the participant and the person obtaining consent (Investigators or designees), and by any other parties required by the EC.

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 participant. 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 participant's medical record.

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

11.5 Confidentiality

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

12 Incidental Findings

Incidental findings (IFs) in clinical research are findings with potential health or reproductive importance that are discovered in the course of conducting the research, but are beyond the aims of the study. IFs in this study may arise from the collecting and analyzing of research images i.e. CXR or PET/CT or in the tests or information collected to determine eligibility criteria i.e. abnormal vital signs, safety bloods, or ECG.

The Principal Investigator is responsible for handling an IF responsibly and promptly and members of the research team will promptly report a suspected IF. If an IF is discovered the PI will inform the participant and exercise his/her judgment on a case by case basis to determine the way forward that is in the best interest of the participant. The PI will make sure that all the necessary documentation for the referral of the participant is put together free of cost to the participant.

13 Publication Policy

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

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.

14 Protocol Amendment Policy

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

Protocol amendments detailing minor administrative changes should be submitted by the Investigator to the EC and regulatory authorities, either for notification purposes or approval as appropriate.

15 Financial Aspects, Insurance and Indemnity

The study Sponsor is the TASK Foundation NPC, funded by the European Union, Horizon 2020.

The participants will not receive any incentives for their involvement in the study. The Sponsor has made provision to reimburse the participants 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.

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