CLINICAL STUDY PROTOCOL

A Phase 1, Partially-Blinded, Placebo-Controlled, Randomized, Multiple Ascending Dose Study to Include A Single Dose Food-Effect Study to Evaluate the Safety, Tolerability, and the Pharmacokinetic Profile of TBI-223 in Healthy Adult Subjects

PROTOCOL NUMBER

TBI-223-CL-002

VERSION 1.0 DATE

15 Dec 2020

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PROTOCOL APPROVAL PAGE

A Phase 1, Partially-Blinded, Placebo-Controlled, Randomized, Multiple Ascending Dose Study to Include A Single Dose Food-Effect Study to Evaluate the Safety, Tolerability, and the Pharmacokinetic Profile of TBI-223 in Healthy Adult Subjects

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PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: Global Alliance for TB Drug Development</td></tr>
<tr><td colspan="2">Name of test product: TBI-223</td></tr>
<tr><td colspan="2">Name of active ingredient: TBI-223</td></tr>
<tr><td colspan="2">Title of study: A Phase 1, Partially-Blinded, Placebo-Controlled, Randomized, Multiple Ascending Dose Study to Include A Single Dose Food-Effect Study to Evaluate the Safety, Tolerability, and the Pharmacokinetic Profile of TBI-223 in Healthy Adult Subjects</td></tr>
<tr><td colspan="2">Principal Investigator: Suraj Kumar Saggar, MD</td></tr>
<tr><td colspan="2">Study Center
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<tr><td>Study period (maximum duration, from screening to study exit): 12 weeks

Food-effect cohorts: approximately 35 days (from check-in [Day -2] through completion of clinical procedures on Day 26, and a follow-up phone call on Day 33).

Non-food-effect cohort: approximately 32 days (from check-in [Day -2] through the completion of clinical procedures on Day 23, and a follow-up phone call on Day 30).

The maximum duration of the study will depend upon the final number and timing of each cohort.</td><td>Phase of development: 1</td></tr>
<tr><td>Duration of treatment:

Cohort 1 and 2 will include single dosing of TBI-223 or placebo for TBI-223 as a single dose fasted (1 day) followed by TBI-223 or placebo for TBI-223 once daily for 14 days under fed conditions. Cohort 3 will be TBI-223 or placebo for TBI-223 once daily for 14 days under fed conditions.</td><td>Number of sites enrolling subjects: 1</td></tr>
</table>

Number of subjects (planned)**:**

Planned to enroll up to 36 subjects in 3 MAD cohorts, each with 12 subjects (9 to receive active drug and 3 to receive placebo).

Additional cohorts (up to 12 subjects per cohort) may be enrolled if deemed appropriate by the Sponsor to study other dose levels, change proposed cohorts, or to study a different dosage formulation. The decision on additional cohorts will not take place until the Sponsor, in conjunction with the Principal Investigator, has determined that adequate safety, tolerability, and pharmacokinetics from the previous cohort have been demonstrated to permit proceeding to the next cohort. The Institutional Review Board (IRB) should be immediately notified of dose escalation decisions or any revised approach for review and approval.

Diagnosis and main criteria for inclusion:

Volunteers will be healthy adult male or female, ages 19 to 50 years (inclusive) at screening, with a body mass index (BMI) $\geq$18.5 and $\leq$32.0 kg.m^2 and body weight of no less than 50.0 kg at the time of screening and check-in, who do not use tobacco or nicotine-containing products. Females subjects may not be pregnant or lactating.

Objectives:

The primary objective of the study is:

- To evaluate the safety and tolerability of multiple doses of TBI-223 in healthy adult subjects

The secondary objective of the study is:

- To determine the pharmacokinetics (PK) of TBI-223 and its metabolite, M2 after multiple ascending doses of TBI-223 in healthy adult subjects when administered after a high-calorie, high-fat meal
- For the TBI-223 sustained-release (SR1) formulation and for the combination of the SR and immediate-release (IR) formulations, to compare the PK profiles of a single dose when administered to healthy adult subjects in the fasting state versus after a high-calorie, high-fat meal
- To determine the pharmacokinetics (PK) of a single dose of the TBI-223 sustained-release (SR1) formulation in healthy adult subjects when administered fasted

Study design overview:

This is a partially-blinded, placebo-controlled, randomized multiple ascending dose (MAD) study to be conducted at one study center.

Thirty-six (36) subjects will be enrolled in 3 cohorts with 12 subjects per cohort. Within each cohort, 9 subjects will be assigned to receive active treatment and 3 subjects will receive placebo. Each subject will participate in one dose level.

The first 2 cohorts (food-effect cohorts) will begin dosing of TBI-223 on Day 1 under fasted conditions, followed by a 3 day washout period and then by multiple doses of TBI-223 administered

after a high-calorie, high-fat meal from Day 4 through Day 17 (total of 14 days). The third cohort (non-food-effect cohort) will begin dosing of TBI-223 on Day 1 and continue through Day 14, all doses administered after a high-calorie, high-fat meal.

Each subject will be administered TBI-223 tablets (SR1 or IR or a combination of both formulations) or placebo once daily for 14 days with corresponding pharmacokinetic measurements. After each dose cohort, the Sponsor and Investigator will review the pharmacokinetic and safety data before proceeding to the next dose level.

Dose escalation to the next cohort (i.e., dose level) or decisions regarding changed or additional cohorts will not take place until the Sponsor, in conjunction with the Principal Investigator and dose escalating committee, has determined that adequate safety, tolerability, and pharmacokinetics from the previous cohort(s) have been demonstrated to permit proceeding to the next cohort. The Institutional Review Board (IRB) should be immediately notified of the dose escalation or any revised approach for review and approval.

Safety will be assessed throughout the study for all subjects. Safety assessments will include physical and detailed neurological examinations, vital signs (blood pressure, pulse rate, respiration rate, temperature and pulse oximetry), electrocardiograms (ECGs), cardiac monitoring, adverse events (AEs), and clinical laboratory tests (including hematology, serology, serum chemistry, coagulation, and urinalysis).

Blood and urine will be collected for clinical laboratory evaluations.

The Principal Investigator, in conjunction with the Sponsor may collect additional blood if necessary, for repeat laboratory or safety evaluations including AE follow up.

Female subjects will have blood collected for serum pregnancy testing. Females claiming postmenopausal status will have blood collected to measure follicle stimulating hormone (FSH) levels.

During each cohort, blood samples (trough samples) will be obtained before each dose of study drug, and at the time points on the events schedule. Plasma pharmacokinetic samples will be analyzed for TBI-223 and M2 using validated analytical methods. Appropriate pharmacokinetic parameters will be calculated using non compartmental methods.

Test product, dosage and mode of administration:

Cohort 1 and 2 will include single dosing of TBI-223 or placebo for TBI-223 as a single dose fasted (1 day) followed by TBI-223 or placebo for TBI-223 once daily for 14 days under fed conditions. Cohort 3 will be TBI-223 or placebo for TBI-223 once daily for 14 days under fed conditions. The following planned dose levels will be orally administered once daily (QD):

Cohort 1 (Food-effect cohort):

Dose Level 1 = 1800 mg TBI-223

1800 mg (3 x 600 mg SR1 tablets or 3 x Placebo tablets)

Day 1: TBI-223 or matching placebo (fasted)

Days 4-17: TBI-223 or matching placebo (fed)

Cohort 2 (Food-effect cohort):

Dose Level 2 = 2400 mg TBI-223

2400 mg (3 x 600 mg SR1 tablets and 1 x 600 mg IR tablets or 4 x Placebo tablets)

Day 1: TBI-223 or placebo (fasted)

Days 4-17: TBI-223 or placebo (fed)

Cohort 3 (Non-food-effect cohort):

Dose Level 3 = 3000 mg TBI-223

3000 mg (4 x 600 mg SR1 tablets and 1 x 600 mg IR tablets or 5 x Placebo tablets)

Days 1-14: TBI-223 or placebo (fed)

Additional cohorts may be enrolled if deemed appropriate by the Sponsor to repeat a dose level or to study another dose level.

Criteria for evaluation:

Safety: Safety assessments will include physical and detailed neurological examinations, vital signs (blood pressure, pulse rate, respiration rate, temperature and pulse oximetry), ECGs, cardiac monitoring, AEs, and clinical laboratory tests (including hematology, serology, serum chemistry, coagulation, and urinalysis). Female subjects will have blood collected for serum pregnancy testing. Females claiming postmenopausal status will have blood collected to measure follicle-stimulating hormone (FSH) levels.

Pharmacokinetics: Pharmacokinetic calculations will be performed using appropriate software, e.g. Phoenix™ WinNonlin® (Version 8.1 or higher, Pharsight Corporation) and/or SAS® (Version 9.4 or higher, SAS Institute Inc.). Pharmacokinetic parameters will be calculated using non-compartmental analysis. The following pharmacokinetic parameters will be determined as appropriate for each study part.

AUC_{Extrap} (%)	The percentage of extrapolated AUC to AUC_{inf} based on extrapolation
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity; calculated as: $AUC_{\inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$
AUC_{last}	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{tau}	Area under the concentration-time curve during the dosing interval
C_{avg}	Average steady-state concentration
C_{last}	The last quantifiable concentration determined directly from individual concentration-time data
CL/F	Apparent total clearance after single administration
CLss/F	Apparent total clearance at steady state
C_{max}	Maximum concentration, determined directly from individual concentration-time data
C_{min}	Minimum concentration
C_{trough}	Trough plasma concentration
R_{AUC}	Accumulation ratio for AUC
R_{Cmax}	Accumulation ratio for C_{max}
T_{last}	Time of the last quantifiable concentration

T_{max}	Time of the maximum concentration
$T_{1/2}$	The observed terminal half-life, calculated as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$
Vz/F	Apparent volume of distribution in the terminal phase
λ_z	The observed terminal rate constant; estimated by linear regression through at least three data points in the terminal phase of the log concentration-time profile

For the non-food-effect cohorts, PK parameters calculated from plasma concentration of TBI-223 and M2 following doses on Days 1 and 14 will include, as appropriate:

- Day 1: AUC_{tau}, C_{max}, C_{24}, C_{avg}, $T_{max.}$ Additionally, AUC_{inf}, AUC_{extrap}, CL/F, V_z/F, λz, and $t_{1/2}$ should be included if $AUC_{tau} \geq 70\%$ of $AUC_{inf.}$
- Day 14: $AUC_{tau,}$ $C_{max,}$ C_{min}, C_{trough} (i.e., C_0), C_{24}, $C_{avg,}$ T_{max}, CL/F, V_z/F, λz, $t_{1/2}$, R_{AUC}, R_{Cmax}

For the food-effect cohorts, PK parameters calculated from plasma concentration of TBI-223 and M2 following doses on Days 1, 4, and 17 will include, as appropriate:

- Day 1: AUC_{tau}, AUC_{extrap}, $AUC_{inf,}$ C_{max}, C_{24}, C_{last}, T_{max}, T_{last}, CL/F, V_z/F, λz, $t_{1/2.}$
- Day 4: AUC_{tau}, C_{max}, C_{24}, $C_{avg,}$ T_{max}. Additionally, AUC_{inf}, AUC_{extrap}, CL/F, V_z/F, λz, $t_{1/2}$ should be included if $AUC_{tau} \geq 70\%$ of $AUC_{inf.}$
- Day 17: $AUC_{tau,}$ $C_{max,}$ C_{min}, C_{trough} (i.e., C_0), C_{24}, $C_{avg,}$ $T_{max,}$ CL/F, V_z/F, λz, $t_{1/2}$, R_{AUC}, R_{Cmax}

Each parameter will be estimated separately for each participant using plasma concentrations of TBI-223 and, as appropriate M2.

Each day one blood sample will be taken immediately before dosing, to measure C_{trough} level and to observe the time that steady state is achieved.

Assessments of food effect will include geometric mean ratios of C_{max} and AUC_{tau} between Day 1 (fasted) and Day 4 (fed), as well as graphical displays of the profiles. Model-based approaches and comparisons with results from the single-dose study, TBI-223-CL-001, may also be undertaken.

Both individual-participant and group summary-statistics (n, mean, median, geometric mean, standard deviation, standard error of the mean, coefficient of variation, minimum, maximum) data will be reported. Summary statistics will be presented by gender. All tests will be performed using a 2-sided α-level of 0.05, and appropriate confidence intervals will be provided.

Efficacy: No efficacy evaluations will be performed in this study.

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the (plasma concentration vs. time) curve
AUC_{last}	area under the curve from time 0 hours to last quantifiable concentration
AUC_{inf}	area under the curve from time 0 hours to infinity
BID	twice daily
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
bpm	beats per minute
Ca	calcium
CFR	Code of Federal Regulations
CFU	colony-forming unit
CI	confidence interval
Cl^-	chloride
C_{last}	last quantifiable drug concentration
CLIA	Clinical Laboratory Improvement Amendments
cm	centimeter(s)
C_{max}	maximum concentration
CNS	central nervous system
CRF	case report form
CYP	cytochrome P450
DMID	Division of Microbiology and Infectious Disease
ECG	electrocardiogram
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
IP	Investigational Product

IRB	institutional review board
IR	Immediate-release
ISF	Investigator Site File
IUD	intrauterine device
K^+	potassium
kg	kilogram(s)
K_3-EDTA	ethylenediaminetetraacetic acid
L	liter(s)
lbs	pounds
LDH	lactate dehydrogenase
m	meter(s)
MAO	monoamine oxidase
max.	maximum
MDR-TB	multidrug resistant tuberculosis
mg	milligram(s)
MICs	minimum inhibitory concentrations
min.	minute(s)
mL	milliliter(s)
mmHg	millimeter of mercury
MPS	mitochondrial protein synthesis
msec	millisecond
Mtb	*Mycobacterium tuberculosis*
Na^+	sodium
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
oz	ounce(s)
PK	pharmacokinetic
PT	prothrombin time
rbc	red blood cell
SAD	Single Ascending Dose
SAE	serious adverse event
SAP	statistical analysis plan
SR	Sustained-release
$T_{½}$ or $t_{½}$	terminal elimination half-life
TB	Tuberculosis
T_{last}	time of the last measurable concentration
T_{max}	time to reach C_{max}
λ_z	apparent elimination rate constant in terminal phase
°C	degrees Celsius/Centigrade

1 INTRODUCTION

1.1 Background Information

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

A brief overview of available confidential information regarding TBI-223 follows below. Unless noted otherwise, the information in this introduction was provided by TB Alliance. Details can be found in the TBI-223 Investigator's Brochure.[1]

1.2 Tuberculosis and Rationale for New Medications

Tuberculosis (TB) in humans is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (Mtb), which typically affects the lungs (pulmonary TB) but can affect other sites as well (extrapulmonary TB). While incidence rates and mortality for TB have been falling, it remains the ninth leading cause of death worldwide, the world's leading cause of death from a single infectious disease, and is responsible for more deaths than human immunodeficiency virus (HIV). In 2016, 6.3 million new cases of TB were reported, with an overall estimated incidence of 10.4 million (World Health Organization [WHO] Global TB Report 2017).

The current TB treatment regimens and treatments for drug-sensitive TB are decades old and are relatively ineffective. The available treatments have a lengthy duration of treatment, can involve multi-drug therapy, many tolerability issues, and require large commitments of resources and infrastructure. High rates of noncompliance are common, which often results in increased mortality, chronic, infectious, and drug-resistant cases. The present TB epidemic and treatment conditions demonstrate the clear need in patients with drug-sensitive or drug-resistant TB for novel drugs and drug regimens that will shorten the current treatment duration and be safe and well tolerated. In addition, new TB drugs and regimens should also be affordable, easy to adopt and implement, suitable for pediatric use and for co-administration with antiretroviral therapy in individuals co-infected with Mtb and HIV. Following the declaration of TB as a global emergency by the WHO in 1993, there has been a resurgence of efforts to develop improved TB therapies and several promising new agents are presently in or approaching clinical evaluation.

TBI-223 like linezolid (Zyvox®), is a novel oxazolidinone antimicrobial that inhibits the growth of Mtb by blocking microbial translation and, thereby, protein synthesis. Linezolid, which is licensed for the treatment of complicated skin infections and hospital-acquired pneumonia (at an adult dose of 600 mg given twice daily [BID] for up to 28 days), has been used to treat difficult cases of multiple drug-resistant and extensively drug-resistant TB with apparent clinical benefit. Since bacterial protein

synthesis is not currently targeted by any of the drugs in the first-line standard of care for treatment of TB (isoniazid, rifampin, pyrazinamide, ethambutol), TBI-223, like linezolid, has no known pre-existing resistance. Therefore, TBI-223 should be effective against multi-drug resistant and extensively drug-resistant forms of TB (MDR-TB and XDR-TB) as well.

The standard dose of linezolid for a multitude of indications is 400 mg or 600 mg BID. Doses of linezolid varying from 300 mg to 1200 mg per day were used to treat pulmonary TB in combination with other TB drugs in novel regimes over periods of up to 20 months with impressive improved outcomes - e.g .in the Nix-TB trial (A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 (Pretomanid) Plus Linezolid in Subjects with Drug Resistant Pulmonary Tuberculosis: NCT02333799), but treatments can be impacted with periods of non-compliance and adverse events, especially neuropathic and myelosuppressive effects. These adverse events are often ameliorated if the dose is reduced or if the drug is discontinued for several weeks and then resumed at a lower dose. Although manageable there is a clear need to develop effective and tolerable oxazolidinones with a better toxicology profile than linezolid.

TBI-223 is a drug candidate from TB Alliance's efforts to develop a safer oxazolidinone with the potential to deliver efficacy similar to linezolid, without the characteristic bone marrow and neuropathic toxicities of the class. It emerged from a scaffold expansion effort based on the linezolid and sutezolid structures. Mammalian mitochondrial protein synthesis (MPS) inhibition is presumed to be the reason for the side effects associated with long-term administration of linezolid, such as anemia, thrombocytopenia, and peripheral neuropathy (Migliori et al., 2009). TBI-223 was tested in an MPS inhibition assay and found to have a half maximal inhibitory concentration (IC_{50}) of 126 µM (46 µg/mL). This concentration exceeds the expected maximum clinical TBI-223 concentration by 2-fold and suggests a lower risk of MPS inhibition. In preclinical studies, TBI-223 showed low minimum inhibitory concentrations (MICs) against Mtb in vitro and efficacy against mouse models of TB as a single agent and in combination with bedaquiline and pretomanid. TBI-223 did not show significant myelosuppression in 28-day Good Laboratory Practice (GLP) toxicity studies in rats and dogs.

Current data suggest that TBI-223 could contribute to a new TB treatment, consistent with the high-priority target product profile for a novel and universal TB drug regimen.

A single ascending dose (SAD) study (TBI-223-CL-001) with TBA-223 has been finalized and the pharmacokinetic and safety data of TBA-223 oral suspension, TBA-223 immediate-release and sustained-release tablets, together with the pre-clinical safety will form the basis for the dose exposures in the clinical study TBI-223-CL-002.

1.3 Preclinical Studies and Toxicity Studies

To support IND filing, a nonclinical development plan has been executed based upon the ICH M3(R2) guidance document, "Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," January 2010.

A series of in vitro and in vivo studies to evaluate the efficacy of TBI-223 were carried out. TBI-223 was evaluated against a large, diverse panel of Mtb clinical isolates, consisting of 96 isolates representative of all identified genetic groups of Mtb, broad geography and diverse drug-susceptibility profiles. The panel included MDR-TB and XDR-TB strains. The MIC of TBI-223 was found to be 1.28 µg/mL for 90% of the strains tested with a range of 0.04 to 5. Like linezolid, TBI-223 demonstrated a mild bactericidal activity against acute mouse infections of TB as a single agent, good activity against chronic mouse infections, including additive activity within the Nix-like drug combination of bedaquiline, an ATP synthase inhibitor, and pretomanid, a nitroimidazole. This combination efficacy demonstrated a strong potential for TBI-223 to replace linezolid in the Nix trial regimen and deliver a universal treatment shortening regimen that is not confined to the XDR-TB population.

A comprehensive battery of in vitro and in vivo safety pharmacology assessments was conducted to characterize the effects of TBI-223 on the function of the nervous, respiratory, and cardiovascular systems. The battery included non-GLP studies of several cardiac ion channels with TBI-223, a GLP human Ether-à-go-go-Related Gene (hERG) assay with TBI-223, a standalone GLP single-dose cardiovascular study. Nervous system and respiratory assessments were conducted in rats administered as single doses of TBI-223.

The pharmacokinetics and oral bioavailability of TBI-223 were evaluated in mice, rats, dogs and monkeys given single or repeated daily doses of TBI-223.

In support of planned human studies, the following toxicology studies have been completed with TBI-223:

- Non-GLP, 4-week, repeat-dose, oral toxicity study in mice.
- Non-GLP, 2- and 4-week, repeat-dose, oral toxicity studies in rats.
- GLP-compliant, 4-week, repeat-dose, oral toxicity study with recovery in rats.
- Non-GLP, 5-day and 2-week, repeat-dose, oral toxicity studies in beagle dogs.
- GLP-compliant, 4-week, repeat-dose, oral toxicity study with recovery in beagle dogs.
- Standard battery of GLP-compliant in vitro and in vivo genetic toxicology studies.

Dogs tolerated doses up to 100 mg/kg/day (50 mg/kg BID) for 28 days but showed dose- and duration-related nervous system effects at repeated doses ≥200 mg/kg/day. There were no correlating histopathology findings in the nervous system in these studies. It is unclear whether the nervous system effects are related to the maximum concentration (C_{max}) or the area under the (plasma concentration vs. time) curve (AUC) of TBI-223.

- In a 5-day study, dogs developed prolonged tremors and two of four dogs were found dead after being given 400 mg/kg/day for 3 days. These dogs had previously been administered 200 mg/kg/day of TBI-223 without clinical signs.
- During the first 4 days of dosing of a 14-day DRF study, tremors and emesis were observed in dogs administered 200 mg/kg/day, and ataxia, prostration, and convulsions were observed in dogs administered 400 mg/kg/day. These dogs were given a 2-day washout period and then dosed at 75 mg/kg/day BID or 150 mg/kg/day QD. Reversible tremors were observed after 8-10 days of dosing at 150 mg/kg/day (QD or 75 mg/kg BID). In the pivotal 28-day dog GLP study, 2 dogs given 200 mg/kg/day (100 mg/kg BID) had continuous tremors after 12 days of dosing.

In ECG evaluation during the pivotal 28-day dog toxicity study, QT prolongation was observed. The findings are detailed below and correlated with similar findings in the GLP cardiovascular safety study in dogs, and likely related to inhibition of the hERG channel observed in the GLP hERG study.

- In dogs administered 200 mg/kg/day (100 mg/kg BID) doses of TBI-223, QT prolongation was observed in the GLP repeat dose toxicology study. The mean QTc interval at 2 to 4 hours post the first daily dose on Day 25 of the dosing phase was longer in males by 23 msec (10%) and in females by 27 msec (11%) administered 200 mg/kg/day compared with the respective controls. Mean uncorrected QT interval was also prolonged (up to 42 msec; 22%). The QT and QTc intervals returned to baseline during the recovery phase.

In addition to the above adverse effects, rats had nonadverse abdominal distension reported in repeat dose studies with TBI-223, and this was associated with food-filled stomach in rats even though they were fasted overnight prior to necropsy.

1.4 Oxazolidinones

The following adverse reactions were noted in more than 1% of adult subjects in a study of different drug in the oxazolidinone class, linezolid (marketed as Zyvox®): headache, diarrhea, nausea, vomiting, dizziness, rash, anemia, taste alteration, vaginal and oral moniliasis, abnormal liver functions tests, fungal infection, tongue discoloration, and abdominal pain.[2]

The Zyvox® label carries warnings and precautions for myelosuppression, peripheral and optic neuropathy, serotonin syndrome, *Clostridium difficile* associated diarrhea, elevated blood pressure in patients with hypertension, lactic acidosis, convulsions, hypoglycemia, and development of drug-resistant bacteria. [2]

1.5 TBI-223 SAD Study Data

TBI-223 Single ascending dose (SAD) study (TBI-223-CL-001)

TBI-223 has been tested in one Phase 1 single-dose ascending dose (SAD) study with healthy volunteers. Study TBI-223-CL-001 was a SAD study designed to evaluate the safety, tolerability, and pharmacokinetics of TBI-223 in healthy adult subjects using an oral suspension, enteric capsule, and Immediate Release (IR) and Sustained Release (SR) tablet formulations.

Part 1 of TBI-223-CL-001 consisted of Cohorts 1-7. Cohorts 1-7 were administered a single dose of 50 to 2600 mg of TBI-223 using the oral suspension. In order to test the absorption in the gastric duodenum, the same subjects of Cohort 3 returned following the completion of Cohort 3 (300 mg suspension), and received TBI-223 as TBI-223 Oral Suspension in oral enteric capsules (300 mg) in an unblinded fashion. Cohort 5 received a single 1200 mg dose of TBI-223 suspension under fed and fasted conditions over two periods. A total of 60 subjects participated in Part 1 of the study.

Part 2 of TBI-223-CL-001 consisted of Cohorts 8 and 9. Cohort 8 consisted of 4 arms, with 6 subjects per arm: In Arms 1-3 of Cohort 8, the 3 SR formulations were administered under fed conditions at 1800 mg, and in Arm 4 the IR tablet was administered under fasting conditions at 2000 mg. In Cohort 9, 6 subjects from Cohort 8, Arm 4, returned to receive the same 2000 mg of the IR tablet under fed conditions. A total of 20 subjects participated in Part 2.

Safety Overview:

Part 1

There were no serious AEs (SAEs) or treatment-emergent adverse event (TEAEs) that led to a subject withdrawal or death.

The most frequently reported TEAE was nausea. There were 5 TEAEs reported by 5 subjects; 2 TEAEs were reported by 2 (33.3%) subjects who received TBI-223, 2000 mg and 3 TEAEs were reported by 3 (37.5%) subjects who received TBI-223 2600 mg.

The second most frequently reported TEAE was dizziness. There were 4 TEAEs reported by 4 subjects; 1 TEAE was report by 1 (14.3%) subject who received TBI-223, 1200 mg (fed), 1 TEAE was reported by 1 (16.7%) subject who received TBI-223, 2000 mg, and 2 TEAEs were reported by 2 (25.0%) subjects who received TBI-223, 2600 mg.

There were no changes in neurological examinations from baseline to 72 hours.

The majority of TEAEs were judged by the Investigator as Grade 1 (mild) in severity. Four subjects experienced Grade 2 (moderate) TEAEs (vomiting, urticaria, hypersensitivity, and blood bilirubin increased).

Overall, 4 (6.5%) subjects reported TEAEs that were judged by the Investigator as probably related to the study treatment, 4 (6.5%) subjects reported TEAEs that were judged as possible, 2 (3.2%) subjects reported TEAEs that were judged as unlikely related, and 5 (8.1%) subjects reported TEAEs that were judged as not related to the study treatment.

All TEAEs reported during Part 1 are shown in the table below.

Table 1 Adverse Events, TEAEs by Primary System Organ Class and Preferred Term, Part 1

MedDRA Primary System Organ Class Preferred Term	Statistic	Placebo (N=14)	TBI-223 50 mg (N=6)	TBI-223 100 mg (N=6)	TBI-223 300 mg (N=6)	TBI-223 300 mg Capsule (N=6)	TBI-223 600 mg (N=6)	TBI-223 1200 mg (Fasted) (N=8)	TBI-223 1200 mg (Fed) (N=7)	TBI-223 2000 mg (N=6)	TBI-223 2600 mg (N=8)	Overall (N=62)
Any TEAE	N (%), No. of Events	4 (28.6), 5	1 (16.7), 1	2 (33.3), 3	1 (16.7), 1	0	0	0	1 (14.3), 1	3 (50.0), 4	3 (37.5), 9	15 (24.2), 24
Gastrointestinal disorders	N (%), No. of Events	0	0	0	0	0	0	0	0	2 (33.3), 2	3 (37.5), 5	5 (8.1), 7
Nausea	N (%), No. of Events	0	0	0	0	0	0	0	0	2 (33.3), 2	3 (37.5), 3	5 (8.1), 5
Vomiting	N (%), No. of Events	0	0	0	0	0	0	0	0	0	2 (25.0), 2	2 (3.2), 2
Nervous system disorders	N (%), No. of Events	0	0	0	0	0	0	0	1 (14.3), 1	1 (16.7), 1	2 (25.0), 3	4 (6.5), 5
Dizziness	N (%), No. of Events	0	0	0	0	0	0	0	1 (14.3), 1	1 (16.7), 1	2 (25.0), 2	4 (6.5), 4
Headache	N (%), No. of Events	0	0	0	0	0	0	0	0	0	1 (12.5), 1	1 (1.6), 1
Cardiac disorders	N (%), No. of Events	0	0	1 (16.7), 1	0	0	0	0	0	0	1 (12.5), 1	2 (3.2), 2
Tachycardia	N (%), No. of Events	0	0	1 (16.7), 1	0	0	0	0	0	0	1 (12.5), 1	2 (3.2), 2

MedDRA Primary System Organ Class Preferred Term	Statistic	Placebo (N=14)	TBI-223 50 mg (N=6)	TBI-223 100 mg (N=6)	TBI-223 300 mg (N=6)	TBI-223 300 mg Capsule (N=6)	TBI-223 600 mg (N=6)	TBI-223 1200 mg (Fasted) (N=8)	TBI-223 1200 mg (Fed) (N=7)	TBI-223 2000 mg (N=6)	TBI-223 2600 mg (N=8)	Overall (N=62)
General disorders and administration site conditions	N (%), No. of Events	0	0	2 (33.3), 2	0	0	0	0	0	0	0	2 (3.2), 2
Energy increased	N (%), No. of Events	0	0	1 (16.7), 1	0	0	0	0	0	0	0	1 (1.6), 1
Medical device site reaction	N (%), No. of Events	0	0	1 (16.7), 1	0	0	0	0	0	0	0	1 (1.6), 1
Skin and subcutaneous tissue disorders	N (%), No. of Events	1 (7.1), 1	1 (16.7), 1	0	0	0	0	0	0	0	0	2 (3.2), 2
Skin discolouration	N (%), No. of Events	1 (7.1), 1	0	0	0	0	0	0	0	0	0	1 (1.6), 1
Urticaria	N (%), No. of Events	0	1 (16.7), 1	0	0	0	0	0	0	0	0	1 (1.6), 1
Vascular disorders	N (%), No. of Events	1 (7.1), 2	0	0	0	0	0	0	0	0	0	1 (1.6), 2
Hypotension	N (%), No. of Events	1 (7.1), 2	0	0	0	0	0	0	0	0	0	1 (1.6), 2
Blood and lymphatic system disorders	N (%), No. of Events	1 (7.1), 1	0	0	0	0	0	0	0	0	0	1 (1.6), 1
Neutropenia	N (%), No. of Events	1 (7.1), 1	0	0	0	0	0	0	0	0	0	1 (1.6), 1
Immune system disorders	N (%), No. of Events	1 (7.1), 1	0	0	0	0	0	0	0	0	0	1 (1.6), 1
Hypersensitivity	N (%), No. of Events	1 (7.1), 1	0	0	0	0	0	0	0	0	0	1 (1.6), 1
Investigations	N (%), No. of Events	0	0	0	1 (16.7), 1	0	0	0	0	0	0	1 (1.6), 1
Blood bilirubin increased	N (%), No. of Events	0	0	0	1 (16.7), 1	0	0	0	0	0	0	1 (1.6), 1
Musculoskeletal and connective tissue disorders	N (%), No. of Events	0	0	0	0	0	0	0	0	1 (16.7), 1	0	1 (1.6), 1

MedDRA Primary System Organ Class Preferred Term	Statistic	Placebo (N=14)	TBI-223 50 mg (N=6)	TBI-223 100 mg (N=6)	TBI-223 300 mg (N=6)	TBI-223 300 mg Capsule (N=6)	TBI-223 600 mg (N=6)	TBI-223 1200 mg (Fasted) (N=8)	TBI-223 1200 mg (Fed) (N=7)	TBI-223 2000 mg (N=6)	TBI-223 2600 mg (N=8)	Overall (N=62)
Back pain	N (%), No. of Events	0	0	0	0	0	0	0	0	1 (16.7), 1	0	1 (1.6), 1

MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0

Cardiac Assessments (ECG and Holter)

Electrocardiograms

There were no clinically significant findings for ECGs.

Heart Rhythm and Cardiac Conduction

In Part 1 of the study, the effect of TBI-223 oral suspension on ECG parameters was evaluated using continuous 12-lead ECG (Holter) monitoring. Serial ECGs were extracted from the Holter recordings at prespecified time points starting on Day –1 through 48 hours post-dose. At baseline, data were available from 6 subjects in each of the 50, 100, 300, 600 and 2000 mg TBI-223 group, 8 subjects in the 1200 and 2600 mg group and from 14 placebo subjects pooled from all cohorts.

TBI-223 Oral Suspension at the studied doses did not have a clinically relevant effect on HR. The pattern across dose groups and relation to the observed PK profile of TBI-223 and M2 do not suggest that the drug or metabolite exert a clinically relevant effect on HR.

In the by-time point analysis for QTcF, mean placebo-corrected ΔQTcF (ΔΔQTcF) ranged from –8.9 ms at 12 hours post-dose in the 600 mg group to 13.3 ms at 5 hours post-dose in the 2000 mg dose group. In the 2 highest dose groups (2000 mg and 2600 mg), mean ΔΔQTcF was 13.1 ms and 13.3 ms at 4 and 5 hours and 12.4 ms at 1 hour post-dose, respectively.

In the concentration-QTc analysis, a full model including TBI-223 and its metabolite M2 was selected as the primary model. The estimated population slope of the concentration-QTc relationship was 0.0004 ms per µg/L (90% CI: -0.00005 to 0.00093) for TBI-223, 0.001 ms per µg/L (90% CI: -0.0010 to 0.0034) for M2 with a treatment effect-specific intercept of 1.6 ms (90% CI: -1.01 to 4.16). The predicted effect on ΔΔQTcF at the geometric mean C_{max} of TBI-223 and of M2 after a single dose of 1200 mg, also accounting for the effect of M2 and TBI-223 at the same time points (T_{max} of TBI-223 and M2, respectively), was 7.47 and 7.16 ms, with an upper bound of the 90% CI of 10.06 and 10.20 ms, respectively. In the concentration-QTc analysis with TBI-223 alone and M2 alone, an effect on ΔΔQTcF can be excluded at TBI-223 and M2 concentrations up to ~8140 µg/L and ~2040 µg/L, respectively.

TBI-223 Oral Suspension at the studied doses did not have a clinically relevant effect on cardiac conduction, i.e., the PR and QRS intervals.

Cardiovascular Summary

In summary, TBI-223 oral suspension at the studied doses had no clinically relevant effects on HR or on cardiac conduction (the PR and QRS intervals). Based on the concentration-QTc analysis, a QTcF effect (ΔΔQTcF) exceeding 10 ms can be excluded for plasma concentrations of TBI-223 and M2 up to ~8000 µg/L and ~2000 µg/L, respectively.

Part 2

There were no SAEs or TEAEs that led to a subject withdrawal or death.

The most frequently reported TEAE was vessel puncture site inflammation. There were 3 TEAEs reported by 3 subjects; 2 TEAEs were reported by 2 (33.3%) subjects who received TBI-223, 1800 mg SR Tablet (Prototype 2, fed), and 1 TEAE was reported by 1 (16.7%) subject who received TBI-223, 2000 mg IR Tablet (fasted).

The second most frequently reported TEAE was dizziness. There were 3 TEAEs reported by 2 subjects; 2 TEAEs were reported by 2 (33.3%) subjects who received TBI-223, 2000 mg IR Tablet (fasted) and 1 TEAE was reported by 1 (16.7%) subject who received TBI-223, 2000 mg IR Tablet (fed).

All TEAEs reported during Part 2 were Grade 1 (mild) in severity.

Overall, 1 (4.2%) subject reported a TEAE that was judged by the Investigator as probably related to the study treatment, 3 (12.5%) subjects reported TEAEs that were judged as possible, and 4 (16.7%) subjects reported TEAEs that were judged as not related to the study treatment.

There were no TEAEs related to clinically significant out-of-range vital sign measurements or laboratory values.

No clinically significant abnormalities in ECGs were observed.

There were no changes in neurological examinations from baseline to 48 hours.

All TEAEs reported during Part 2 are shown in the table below.

Table 2 Adverse Events, TEAEs by Primary System Organ Class and Preferred Term, Part 2

MedDRA Primary System Organ Class Preferred Term	Statistic	TBI-223 1800 mg SR-1 tablet (Fed) (N=6)	TBI-223 1800 mg SR-2 tablet (Fed) (N=6)	TBI-223 1800 mg SR-3 tablet (Fed) (N=6)	TBI-223 2000 mg IR tablet (Fasted) (N=6)	TBI-223 2000 mg IR tablet (Fed) (N=6)	Overall (N=24)
Any TEAE	N (%), No. of Events	1 (16.7), 1	2 (33.3), 2	2 (33.3), 3	3 (50.0), 6	2 (33.3), 2	8 (33.3), 14
General disorders and administration site conditions	N (%), No. of Events	0	2 (33.3), 2	2 (33.3), 3	1 (16.7), 2	0	5 (20.8), 7
Vessel puncture site inflammation	N (%), No. of Events	0	2 (33.3), 2	0	1 (16.7), 1	0	3 (12.5), 3
Chest discomfort	N (%), No. of Events	0	0	0	1 (16.7), 1	0	1 (4.2), 1
Vessel puncture site pain	N (%), No. of Events	0	0	1 (16.7), 1	0	0	1 (4.2), 1
Vessel puncture site reaction	N (%), No. of Events	0	0	1 (16.7), 1	0	0	1 (4.2), 1
Vessel puncture site swelling	N (%), No. of Events	0	0	1 (16.7), 1	0	0	1 (4.2), 1
Nervous system disorders	N (%), No. of Events	1 (16.7), 1	0	0	3 (50.0), 3	1 (16.7), 1	4 (16.7), 5
Dizziness	N (%), No. of Events	0	0	0	2 (33.3), 2	1 (16.7), 1	2 (8.3), 3
Disturbance in attention	N (%), No. of Events	0	0	0	1 (16.7), 1	0	1 (4.2), 1
Headache	N (%), No. of Events	1 (16.7), 1	0	0	0	0	1 (4.2), 1
Gastrointestinal disorders	N (%), No. of Events	0	0	0	1 (16.7), 1	1 (16.7), 1	1 (4.2), 2
Abdominal pain	N (%), No. of Events	0	0	0	0	1 (16.7), 1	1 (4.2), 1
Nausea	N (%), No. of Events	0	0	0	1 (16.7), 1	0	1 (4.2), 1

MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0.

Safety Summary:

Part 1

In part 1 of the study all subjects were dosed with TBI-223 oral suspension.

Overall, TBI-223 was well-tolerated when administered as an oral suspension and oral enteric capsules in healthy subjects under fed and fasted conditions at doses from 50 mg to 2600 mg. At 2600 mg of the oral suspension, the arithmetic mean C_{max} of TBI-223 was 16.2 µg/mL. Two of six subjects had C_{max} exceeding 20 µg/mL (21.0 and 22.0 µg/mL). The arithmetic mean $AUC_{0\text{-}inf}$ of TBI-223 was 127 µg.h/mL, with the maximum value being 190 µg.h/mL.

Part 2

In Part 2 of the study all subjects were dosed with TBI-223 Immediate (IR) and Sustained (SR) release formulations.

Overall, the TBI-223 was well-tolerated when administered as a tablet formulation in healthy subjects under fed and fasted conditions at doses of 2000 mg (IR) and 1800 mg (SR). The highest concentrations of TBI-223 were seen with 2000 mg IR under fed conditions, where the arithmetic mean C_{max} was 19.7 µg/mL and where two of six subjects had C_{max} exceeding 20 µg/mL (25.9 and 27.5 µg/mL). That group also experienced the highest arithmetic mean $AUC_{0\text{-}inf}$ of TBI-223, 100 µg.h/mL, with the maximum value being 150 µg.h/mL.

Pharmacokinetic Summary (Suspension):

Single Ascending TBI-223 Doses, Cohorts 1-7, Fasted (Part 1)

After administrations of single TBI-223 oral suspension doses under fasted conditions, median TBI-223 T_{max} ranged from 1.00 h (Cohort 1, 50 mg) to 2.25 h (Cohort 7, 2600 mg). TBI-223 exposure (C_{max} and AUCs) increased in a nearly dose-proportional manner with an increase in dose under fasted conditions dose over the 50 mg to 2600 mg dose range. Slope (β_1) were close to 1 for each parameter and the 90% confidence intervals nearly included 1. Slope estimates and 90% confidence intervals (90% CI) were 0.9310 (0.8622 - 0.9997) for C_{max}, 1.1385 (1.0906 – 1.1863) for $AUC_{0\text{-}t}$, and 1.1338 (1.0853 – 1.1823) for $AUC_{0\text{-}inf}$.

Formulation Effect, Cohort 3, 300 mg, Capsule vs. Oral Suspension (Part 1)

Median TBI-223 T_{max} was observed at approximately 3.6 h later for the TBI-223 capsule formulation (5.00 h) compared to that after the oral suspension (1.37 h). Maximum TBI-223 exposure (C_{max}) was approximately 58% lower after administration of the capsule formulation compared to that after the oral suspension formulation; total TBI-223 exposure (AUCs) was similar for capsule and oral suspension formulations. This outcome demonstrated uptake in the duodenum and therefore supported evaluating a sustained release formulation which could result in more T>MIC Geometric mean ratios and 90% CIs for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ were 42.46% (31.57% - 57.10%), 94.43% (90.28% - 98.76%), and 94.73% (90.58% - 99.06%), respectively.

Food Effect, Cohort 5, TBI-223 Oral suspension 1200 mg; (Part 1)

Median T_{max} was 1.50 h after drug administration under fed and fasted conditions. Maximum and total TBI-223 exposure (C_{max} and AUCs) were similar for fed and fasted conditions. Geometric mean ratios and 90% CIs for C_{max}, AUC_{0-t}, and AUC_{0-inf} were 103.34% (87.00% - 122.75%), 103.23% (97.80% - 108.96%), and 102.79% (96.37% - 109.64%), respectively.

Food Effect, TBI-223 IR Tablets, 2000 mg; (Part 2)

Administration of IR tablets with food delayed TBI-223 T_{max} by approximately 1 h. Administration of TBI-223 IR tablets (2000 mg) with food increased TBI-223 C_{max} by approximately 51%. TBI-223 AUCs were slightly higher (~16%) under fed conditions compared to that under fasted conditions. Geometric mean ratios and 90% CIs for C_{max}, AUC_{0-t}, and AUC_{0-inf} were 151.24% (127.91% - 178.82%), 115.73% (112.08% - 119.50%), and 115.70% (112.06% - 119.47%), respectively.

Different Formulation (Tablets - Immediate and Sustained release) Pharmacokinetics:

Sustained-release (SR) Tablet Prototypes 1, 2, and 3 (Fed), 1800 mg vs. IR Tablets 2000 mg (Fasted), (Part 2)

Median TBI-223 T_{max} was observed approximately 4.5 to 5.5 h later for the SR prototypes administered with food compared to the IR formulation under fasted conditions.

Maximum TBI-223 exposure (normalized C_{max}) was approximately 46%, 28%, and 34% lower after administrations of SR-1, SR-2, and SR-3 under fed conditions, compared to IR tablet under fasted conditions. Total TBI-223 exposure (normalized AUC_{0-t} and AUC_{0-inf}) was approximately 19% lower for SR-1 and SR-2 administered under fed conditions compared to IR tablets administered under fasted conditions; AUCs were similar for SR-3 and IR.

Geometric mean ratios and 90% CIs for SR-1 normalized C_{max}, AUC_{0-t}, and AUC_{0-inf} were 53.53% (40.10% - 71.45%), 81.11% (62.92% - 104.56%), and 81.52% (63.26% - 105.04%), respectively. Geometric mean ratios and 90% CIs for SR-2 normalized C_{max}, AUC_{0-t}, and AUC_{0-inf} were 71.70% (53.71% - 95.71%), 80.55% (62.49% - 103.84%), and 80.56% (62.51% - 103.81%), respectively. Geometric mean ratios and 90% CIs for SR-3 normalized C_{max}, AUC_{0-t}, and AUC_{0-inf} were 66.31% (49.67% - 88.53%), 95.71% (74.25% - 123.38%), and 95.73% (74.29% - 123.35%), respectively.

Sustained-release (SR) Tablet Prototypes 1, 2, and 3 (Fed), 1800 mg vs. IR Tablets 2000 mg (Fed), (Part 2)

Median TBI-223 T_{max} was observed approximately 3.5 to 4.5 h later for the SR prototypes compared to the IR formulation under fed conditions.

Maximum TBI-223 exposure (normalized C_{max}) was approximately 65%, 53%, and 56% lower after administrations of SR-1, SR-2, and SR-3 compared to IR tablet under fed conditions. Total TBI-223 exposure (normalized AUC_{0-t} and AUC_{0-inf}) was approximately 17%-30% lower after administrations of SR-1, SR-2, and SR-3 compared to IR tablet under fed conditions.

Geometric mean ratios and 90% CIs for SR-1 normalized C_{max}, AUC_{0-t}, and AUC_{0-inf} were 35.39% (26.04% - 48.10%), 70.09% (54.10% - 90.81%), and 70.45% (54.40% - 91.24%), respectively. Geometric mean ratios and 90% CIs for SR-2 normalized C_{max}, AUC_{0-t}, and AUC_{0-inf} were 47.41% (34.88% - 64.43%), 69.60% (53.72% - 90.18%), and 69.62% (53.76% - 90.17%), respectively. Geometric mean ratios and 90% CIs for SR-3 normalized C_{max}, AUC_{0-t}, and AUC_{0-inf} were 43.85% (32.26% - 59.59%), 82.70% (63.83% - 107.15%), and 82.74% (63.88% - 107.15%), respectively.

1.6 Adverse Effects, Warnings, and Precautions

Given the key safety findings in the SAD (TBI-223) study, TBI-223-CL-001 and nonclinical safety studies for the cardiovascular system (prolonged QTc) and the nervous (CNS) system (tremors), we will implement the following monitoring procedures.

Cardiovascular Monitoring

Cardiovascular monitoring will be conducted and include the following at both protocol-defined time points and whenever deemed necessary by the study investigator. Subjects treated with TBI-223 will have their ECGs evaluated prior to treatment and during treatment. During treatment, the timing of ECGs will be guided by pharmacokinetic (PK) data so that collection occurs around the estimated T_{max}.

ECGs will be interpreted and signed and dated by the Principal Investigator or designee. The ECGs will be classified as normal, having a clinically insignificant abnormality, or having a clinically significant abnormality. All clinically significant abnormalities will be recorded as AEs. In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected and uncorrected) will be noted on the case report form (CRF). If a patient's corrected QT interval (QTcF) exceeds 500 msec while on treatment or there is a change from baseline exceeding 60 msec, TBI-223 administration should be stopped, and the patient monitored with ECGs and/or telemetry until the QTcF returns to pre-treatment levels.

Central Nervous System Monitoring

A detailed neurological exam will be conducted and include the following at both protocol-defined time points and whenever deemed necessary by the study investigator:

- Mental status – assessment of orientation, speech, and memory

- Cranial nerves – assessment of cranial nerves II-XII, excluding fundoscopic examination
- Motor system – brief assessment of tone and strength
- Sensory system – brief survey for light touch and temperature of the face, neck, arms, trunk, and legs
- Reflexes – assessment of deep tendon reflexes and plantar responses (Babinski sign)
- Coordination – assessment of upper and lower extremities, including assessment for tremor
- Gait – assessment of tandem gait

1.7 Overview and Dose Rationale

TBI-223, as a single agent at 100 mg/kg, demonstrated moderate activity against acute murine TB in BALB/c mice, and in a C3HeB/FeJ mouse model of TB. When combined with the TB drug bedaquiline and the investigational TB drug pretomanid, TBI-223 at 100 mg/kg demonstrated bactericidal and sterilizing activity against murine TB in BALB/c mice that was similar to that of linezolid at the same dose (100 mg/kg). The PK exposure at 100 mg/kg was 179 µg•hr/mL, with T>MIC at 61% (or 14.6 hr/day) in the female BALB/c mice.

A dose fractionation study of TBI-223 in a BALB/c mouse model of TB showed that the efficacy drivers were AUC ($R^2 = 0.92$) and T>MIC ($R^2 = 0.83$). The study indicated that a 2 Log lung colony-forming unit (CFU) reduction can be achieved with total a weekly AUC of 868 µg.hr/mL, or daily $AUC_{0\text{-}24hr}$ of 124 µg.hr/mL, with T>MIC of 34% (T>MIC at 8.2 hours over 24 hours).

The QD dose regimens in this study were selected to achieve high AUC and T>MIC. For the latter objective, the SR formulation introduced in the SAD study (called SR-1 there) will comprise the majority component of a QD regimen. The SAD study showed that such a formulation yields an AUC 70% that of an IR tablet at an equivalent dose under fed conditions, while the C_{max} ratio is only 35%. The SR dosages planned for this study are 1800 and 2400 mg. T_{max} for the SR and IR tablet was at 7 and 3 hours, respectively. To boost exposure during the prolonged absorption phase of the SR tablet, a single 600 mg IR tablet will here be added to each of the SR dosages, yielding total doses of 1800, 2400, and 3000 mg. Simulations predict that the steady-state C_{max} of the average concentration for those three regimens will be 5.7, 7.9, and 9.7 µg/mL, respectively, below the lowest preclinical no adverse effect level of 20.2 µg/mL and below the highest arithmetic mean C_{max} seen in the SAD study, 19.7 µg/mL. Expected values of steady-state $AUC_{0\text{-}24h}$ are 63.8, 93.9, and 115.2 µg.h/mL, the higher values being similar to the highest arithmetic mean $AUC_{0\text{-}inf}$ seen in the SAD study, 100 µg.h/mL. Expected T>MICs are 70, 85, and 93%. If successful, the QD regimens produced here by the pairing of SR and IR tablets may be implemented in a single

formulation such as a bilayer tablet. Once again, below are the predicted exposures of proposed doses in table format (Table 3).

Table 3 Exposures

Cohort	Dose (QD)	C_{max}	$AUC_{(0\text{-}24hr)}$	%T>MIC
Cohort 1	1800 mg (3 x 600 mg SR1)	5.7 µg/mL	63.8 (h*µg/mL)	70%
Cohort 2	2400 mg (3 x 600 mg SR1 and 1 x 600 mg IR)	7.9 µg/mL	93.9 (h*µg/mL)	85%
Cohort 3	3000 mg (4 x 600 mg and 1 x 600 mg IR)	9.7 µg/mL	115.2 (h*µg/mL)	93%

2 OBJECTIVE

The primary objective of the study is:

- To evaluate the safety and tolerability of multiple doses of TBI-223 in healthy adult subjects.

The secondary objectives of the study are:

- To determine the pharmacokinetics (PK) of TBI-223 and its metabolite M2 after multiple ascending doses of TBI-223 in healthy adult subjects when administered after a high-calorie, high-fat meal
- For the TBI-223 sustained-release (SR) formulation and for a combination of the SR and immediate-release (IR) formulations, to compare the PK profiles of a single dose when administered to healthy adult subjects in the fasting state versus after a high-calorie, high-fat meal
- To determine the pharmacokinetics (PK) of a single dose of the TBI-223 sustained-release (SR1) formulation in healthy adult subjects when administered fasted.

3 STUDY DESIGN SUMMARY

This is a partially-blinded, placebo-controlled, randomized multiple ascending dose (MAD) study to be conducted at one study center.

Thirty-six (36) subjects will be enrolled in 3 cohorts with 12 subjects per cohort. Within each cohort, 9 subjects will be assigned to receive active treatment and 3 subjects will receive placebo. Each subject will participate in one dose level.

The first 2 cohorts (food-effect cohorts) will begin dosing of TBI-223 on Day 1 under fasted conditions, followed by a 3 day washout period and then followed by multiple doses of TBI-223 administered after a high-calorie, high-fat meal from Day 4 through Day 17 (total of 14 days). The third cohort (non-food-effect cohort) will begin dosing of TBI-223 on Day 1 and continue through Day 14, all doses administered after a high-calorie, high-fat meal.

Each subject will be administered TBI-223 or matching placebo with corresponding pharmacokinetic measurements. After each dose cohort, the Sponsor and Investigator will review the pharmacokinetic and safety data before proceeding to the next dose level.

Dose escalation to the next cohort (i.e., dose level) or decisions regarding changed or additional cohorts will not take place until the Sponsor, in conjunction with the Principal Investigator and dose escalating committee, has determined that adequate safety, tolerability, and pharmacokinetics from the previous cohort(s) have been demonstrated to permit proceeding to the next cohort. The Institutional Review Board (IRB) should be immediately notified of the dose escalation or any revised approach for review and approval.

Safety will be assessed throughout the study for all subjects. Safety assessments will include physical and detailed neurological examinations, vital signs (blood pressure, pulse rate, respiration rate, temperature and pulse oximetry), ECGs, cardiac monitoring, adverse events (AEs), and clinical laboratory tests (including hematology, serology, serum chemistry, coagulation, and urinalysis).

Blood and urine will be collected for clinical laboratory evaluations.

The Principal Investigator, in conjunction with the Sponsor may collect additional blood if necessary, for repeat laboratory or safety evaluations including AE follow up.

Female subjects will have blood collected for serum pregnancy testing. Females claiming postmenopausal status will have blood collected to measure follicle stimulating hormone (FSH) levels.

During each cohort, blood samples (trough samples) will be obtained before each dose of study drug, and at the time points on the events schedule (Table 6 for food-effect cohorts and Table 7 for non-food-effect cohort). Plasma pharmacokinetic samples will be analyzed for TBI-223 and M2 using validated analytical methods. Appropriate pharmacokinetic parameters will be calculated using non compartmental methods.

An overview of the dose cohorts is presented in Table 5.

Table 4 Dose Cohorts

Cohort[a]	Dose	
1	Day 1: Single dose of TBI-223, 1800 mg (n=9) (3 x 600 mg SR1 tablets)	Day 1: Single dose of Placebo, 1800 mg (n=3) (3 x placebo tablets for 600 mg IR and SR)
1	Day 4: 14 doses (1 per day) of TBI-223, 1800 mg (n=9) (3 x 600 mg SR1 tablets)	Day 4: 14 doses (1 per day) of Placebo, 1800 mg (n=3) (3 x placebo tablets for 600 mg IR and SR)
2	Day 1: Single dose of TBI-223, 2400 mg (n=9) (3 x 600 mg SR1 tablets and 1 x 600 mg IR tablet)	Day 1: Single dose of Placebo, 2400 mg (n=3) (4 x placebo tablets for 600 mg IR and SR)
2	Day 4: 14 doses (1 per day) of TBI-223, 2400 mg (n=9) (3 x 600 mg SR1 tablets and 1 x 600 mg IR tablet)	Day 4: 14 doses (1 per day) of Placebo, 2400 mg (n=3) (4 x placebo tablets for 600 mg IR and SR)
3	Day 1: Single doses (1 per day) of TBI-223, 3000 mg (n=9) (4 x 600 mg SR1 tablets and 1 x 600 mg IR tablet)	Day 1: 14 doses (1 per day) of Placebo, 3000 mg (n=3) (5 x placebo tablets for 600 mg IR and SR)

a) Additional cohorts may be enrolled if deemed appropriate by the Sponsor to repeat a dose level or to study another dose level.

3.1 Dose Escalation

Dose Escalation Review

The review of all pertinent safety/tolerability data will include physical examinations, ECGs, vital signs, clinical laboratory tests, cardiac monitoring, and adverse events (AEs or SAEs) through Day 30 (non-food-effect cohort) or Day 33 (food-effect cohorts). Data considered will include data from the current dose cohort and all previous cohorts. The Sponsor and Investigator will determine if there is sufficient data available from all participating subjects to make a dose escalation decision.

Any AEs of grade ≥ 2 toxicities (per DMID toxicity table; Appendix 3) must be discussed in the determination of escalation to the next dose level. PK analysis will be completed only on the active treatment subjects and will be blinded by subject. ECG

data will be analyzed in a blinded fashion and unblinded by ECG vendor in order to be presented by treatment group in aggregate (reviewers will not be unblinded by subject).

Upon review of relevant cohort data, the Sponsor, in conjunction with the Investigator, may decide to:

1. Escalate the dose as planned.
2. Evaluate an intermediate dose level prior to proceeding to the next planned dose level based on PK and safety data of preceding groups.
3. Repeat a given dose level in a new cohort of subjects.
4. Increase the dose of the next cohort if the PK is lower than expected in the previous cohort.
5. Add a cohort if the PK is lower than expected after a cohort and there are no safety concerns.
6. Halt the study.

3.2 Cohort Stopping Rules for Subjects Receiving Active Drug:

If any of the cohort stopping rules are met, cohort dosing must be stopped until review of the data by the Sponsor and the Investigator.

Rules for stopping dosing of a cohort include the following:

1. One subject experiences a drug-related SAE.
2. Two or more subjects develop Grade 3 or higher central nervous system AE considered related to drug.
3. Two or more (≥2) subjects develop QTcF > 500 msec with an increase from baseline > 60 msec after completion of repeat testing.
4. Two or more subjects experience confirmed Grade 3 or Grade 4 cardiac rhythm disturbances considered related to drug.

If any of the cohort stopping rules are met, cohort dosing must be stopped until the data has been reviewed by the Sponsor, Investigator and Dose Escalating meeting (DEM) before dosing is resumed, or other actions taken, or the decision made to discontinue the cohort. Refer to Section 6.2.5 for unblinding procedures. The IRB or Ethics committee (EC) should be immediately notified according to their regulations.

4 IDENTITY OF INVESTIGATIONAL PRODUCT

The Investigational Medicinal Product (IMP) will be supplied as TBI-223 tablets or placebo in the following dose strengths and formulations: TBI-223 SR Tablets, 600 mg

(Prototype 1; SR1), TBI-223 IR Tablets, 600 mg (IR), and Placebo Tablets for TBI-223 IR and SR Tablets, 600 mg (Placebo).

Refer to Appendix 2 for details regarding the description and composition of TBI-223.

Table 5 Identity of Investigational Products

Test Products:	TBI-223 SR1 Tablet, 600 mg
	Manufactured for Global Alliance for TB Drug Development
	and
	TBI-223 IR Tablet, 600 mg
	Manufactured for Global Alliance for TB Drug Development

Control Product:	Placebo Tablet for TBI-223 IR and SR Tablets, 600 mg
	Manufactured for Global Alliance for TB Drug Development

5 SUBJECT SELECTION

5.1 Inclusion Criteria

All volunteers must satisfy the following criteria to be considered for study participation:

1. Understands study procedures and voluntarily provides written informed consent prior to the start of any study-specific procedures.
2. Is a healthy adult male or a healthy adult female of non-childbearing potential, 19 to 50 years of age (inclusive) at the time of screening.
3. Has a body mass index (BMI) $\geq$18.5 and $\leq$32.0 (kg/m^2) and a body weight of no less than 50.0 kg at the time of screening and check-in.
4. Is medically healthy with no clinically significant screening results, as determined by the Principal Investigator (e.g., laboratory profiles are normal up to and including Grade 1 per DMID toxicity tables; Appendix 3), medical history, vital signs, ECG, or physical/neurological examination findings. Note: If exclusionary lab criteria are met, values may be confirmed by repeat evaluation.
5. Has not used tobacco- or nicotine-containing products (including smoking cessation products), for a minimum of 6 months before dosing.
6. Females of non-childbearing potential, based on having undergone one of the following sterilization procedures at least 6 months before dosing:
    - Hysteroscopic sterilization.
    - Bilateral tubal ligation or bilateral salpingectomy;
    - Hysterectomy; or

- Bilateral oophorectomy.
- Or is postmenopausal with amenorrhea for at least 1 year before the first dose with serum FSH levels consistent with postmenopausal status (i.e., greater than 40 mIU/mL) at screening.

Or, if female of childbearing potential, must agree to use an allowable form of birth control from screening until 14 days after study completion. The following are allowed birth control methods for this study:

- Vasectomized partner (at least 6 months before dosing);
- Non-surgical permanent sterilization (e.g., Essure® procedure) at least 3 months before dosing.
- Double barrier method (e.g., diaphragm with spermicide; condoms with spermicide).
- Intrauterine device (IUD).
- Abstinence (and must agree to use a double barrier method if they become sexually active during the study);
- Implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months before study dosing; and/or
- Oral, patch, or injected contraceptives, or vaginal hormonal device (i.e. NuvaRing®), in use for at least 3 consecutive months before study dosing.

7. If a non-vasectomized male (or male vasectomized less than 120 days prior to study start) must agree to the following during study participation and for 90 days after the last administration of study drug:
   - Use a condom with spermicide while engaging in sexual activity or be sexually abstinent
   - Not donate sperm during this time.

   In the event the sexual partner is surgically sterile or postmenopausal, use of a condom with spermicide is not necessary. None of the birth control restrictions listed above are required for vasectomized males whose procedure was performed more than 120 days before study start.
8. Is willing to answer inclusion and exclusion criteria questionnaire at check-in.
9. Is able to comply with the protocol and the assessments therein, including all restrictions.

10. Is willing and able to remain in the study unit for the entire duration of the assigned confinement period(s), return for outpatient visit(s), and receive a phone call for follow-up questioning about AEs.

5.2 Exclusion Criteria

Volunteers will be excluded from study participation for any of the following:

1. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, neurological (including epilepsy), oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
2. Any abnormality on neurologic exam.
3. History of any illness that, in the opinion of the Investigator, might confound the results of the study or pose an additional risk to the subject by their participation in the study.
4. Surgery within the past 90 days prior to dosing as determined by the Investigator to be clinically relevant, or any history of cholecystectomy.
5. History or presence of alcoholism or drug abuse within the past 2 years as determined by the Investigator to be clinically relevant.
6. History of sensitivity or contraindication to use of linezolid, tedizolid, or any study investigational products.
7. Participation in another clinical trial within 30 days prior to dosing.
8. Female subjects who are pregnant or lactating.
9. Positive result on a urine drug/alcohol/cotinine screen at Baseline or check-in.
10. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening. Out-of-range vital signs may be repeated once for confirmation.
11. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening. Out-of-range vital signs may be repeated once for confirmation.
12. Any clinically significant ECG abnormality at Screening (as deemed by decision of the Investigator and the Sponsor's Medical Monitor).

    NOTE: The following may be considered not clinically significant without consulting the Sponsor's Medical Monitor:

    - Mild first-degree A-V block (P-R interval <0.23 sec)
    - Right or left axis deviation

- Incomplete right bundle branch block
- Isolated left anterior fascicular block (left anterior hemiblock) in younger athletic subjects
- Early repolarization
- Tall T waves
- RSR in V1/V2 consistent with right ventricular conduction delay (with acceptable QRS)
- Sinus rhythm or sinus bradycardia with sinus arrhythmia
- Minimal or moderate voltage criteria for left ventricular hypertrophy (LVH).

13. QTcF interval >450 msec for males or >470 msec for females at screening, Day -1, or Day 1 (predose), or history of prolonged QT syndrome. For the triplicate ECGs taken at screening and on Day -1, the average QTcF interval of the three ECG recordings will be used to determine qualification.
14. Family history of long-QT syndrome or sudden death without a preceding diagnosis of a condition that could be causative of sudden death (such as known coronary artery disease, congestive heart failure, or terminal cancer).
15. History of any of the following:
    - Serotonin syndrome
    - Seizures or seizure disorders, other than childhood febrile seizures
    - Brain surgery
    - History of head injury in the last 5 years
    - Any serious disorder of the nervous system particularly one that may lower the seizure threshold.
16. Lactose intolerant.

Specific Treatments

17. Use of any prescription medication within 14 days prior to dosing.
18. Use of any of the following medications within 30 days before the first dose of study drug or during the study drug treatment period: monoamine oxidase (MAO) inhibitors (phenelzine, tranylcypromine), tricyclic antidepressants (amitriptyline, nortriptyline, protriptyline, doxepin, amoxapine, etc.), antipsychotics such as chlorpromazine and buspirone, serotonin re-uptake inhibitors (fluoxetine, paroxetine, sertraline, etc.), bupropion, agents known to prolong the QTc interval

(erythromycin, clarithromycin, astemizole, type Ia [quinidine, procainamide, disopyramide] and III [amiodarone, sotalol] anti-arrhythmics, carbamazepine, sulfonylureas, and meperidine).

19. Use of any over-the-counter (OTC) medication, including herbal products and vitamins, within 7 days prior to dosing, except acetaminophen. Up to 3 grams per day of acetaminophen is allowed at the discretion of the Investigator prior to dosing.
20. Use of any drugs or substances known to be significant inhibitors of cytochrome P450 (CYP) enzymes and/or significant inhibitors or substrates of P-glycoprotein (P-gp) and/or organic anion transporting polypeptides (OATP) within 14 days prior to the first dose of study drug.
21. Use of any drugs or substances known to be inducers of CYP enzymes and/or Pgp, including St. John's Wort, within 30 days prior to the first dose of study drug.
22. Use of any drugs or substance known to lower the seizure threshold.

Specific Laboratory Abnormalities

23. Serum magnesium, potassium, or calcium laboratory values outside of the normal range at screening. If exclusionary lab criteria are met, values may be confirmed by repeat evaluation.
24. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV).
25. ALT or AST greater than ULN.

5.3 Medication and Activity Restrictions

1. Subject must not donate blood from 56 days or plasma from 7 days prior to the first dose of study medication until after the follow-up phone call. It is recommended that blood/plasma donations not be made for at least 30 days after discharge from the clinic.
2. Subject must not use tobacco- or nicotine-containing products (including smoking cessation products) from 6 months prior to the first dose of study medication until after the follow-up phone call.
3. Subjects must not consume alcohol from 72 hours prior to the first dose of study medication until after the follow-up phone call.
4. Subject must not consume beverages or foods that contain grapefruit or Mandarin oranges from 10 days before the first dose of study medication, or poppy seeds, broccoli, Brussels sprouts, pomegranate, star fruit, char grilled meat, or caffeine/xanthine from 48 hours before the first dose of study medication, until

after discharge from the clinic. Subjects will be instructed not to consume any of the above products; however, allowance for an isolated single incidental consumption may be evaluated and approved by the study Investigator based on the potential for interaction with the study drug.

5. Subject should avoid large quantities of foods or beverages with high tyramine content 48 hours prior to the first dose of study medication until discharge from the clinic. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); and soy sauce (5 mg tyramine per 1 teaspoon). The tyramine content of any protein rich food may be increased if stored for long periods or improperly refrigerated.
6. Subject must not engage in strenuous exercise from 48 hours prior to the first dose of study medication until after discharge from the clinic.
7. Subject must be willing to remove any artificial nails (e.g., acrylic, gel) or fingernail polish and not use such products for the duration of the study.
8. Subject must not take any adrenergic/serotonergic agonists, such as pseudoephedrine and phenylpropanolamine (frequently found in cold and cough remedies), within 7 days before the first dose of study drug or during the study drug treatment period.

5.4 Screening

The informed consent documents will be discussed with each potential participant, and each individual will sign an informed consent document for the study prior to any study-specific procedures being performed.

Each potential study participant will have the following assessments by the Investigator or designee within 28 days prior to study start:

- Demographic data, including sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), and smoking habits.
- Medical history
- Serology tests for HIV, hepatitis B and C
- Clinical laboratory tests (hematology, chemistry, and urinalysis)
- Coagulation test
- Serum pregnancy (all female subjects)
- FSH test (female subjects claiming post-menopausal status)
- Urine test for drugs of abuse, alcohol, and cotinine

- Physical and neurological examinations
- Triplicate 12-lead safety ECGs
- Vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry)
- Concomitant medication review

Only medically healthy subjects with clinically acceptable laboratory profiles and ECGs within the defined parameters who fulfill all other inclusion criteria and meet none of the exclusion criteria outlined in the previous sections will be enrolled in the study.

Subjects will be assigned numbers in an ascending order, based on successful completion of the screening process.

6 STUDY PROCEDURES

6.1 Subject Assignment

Thirty-six (36) subjects are planned to be enrolled in the study, 12 subjects per cohort. Additional subjects may be enrolled if deemed appropriate by the Sponsor to repeat a dose level or to study another dose level. The number of subjects for each cohort is expected to provide sufficient safety and tolerability data to evaluate whether escalation to the next dose level is warranted. This study has not been formally powered.

Each subject will receive an assigned treatment (active or placebo) based on the randomization schedule prepared by the unblinded statistician. The unblinded pharmacy staff will ensure compliance with the randomization schedule.

6.2 Blinding

All subjects and clinical staff (except for the unblinded pharmacy staff) will be blinded to treatment. An unblinded pharmacy staff will be required at the Clinical Site to comply with the study's randomization and blinding requirements. At the Clinical Site, prior to study initiation, the Principal Investigator will be responsible for designating a qualified pharmacy staff to serve as the unblinded pharmacy staff in the study. Unblinded pharmacy staff may dose subjects but may not participate in any subject assessments.

Throughout the study, the designated unblinded pharmacy staff will be responsible for all drug accountability issues, including preparing, labeling, dispensing, and dosing study drug according to the randomization code provided, yet remain independent of all subject assessments. The pharmacy staff will follow the Standard Operating Procedures and Work Instructions related to pharmacy services and protocol-specific requirements.

Randomization codes will be provided to the unblinded pharmacy staff. Confirmation of receipt of the randomization code will be required by the Sponsor. The unblinded

pharmacy staff will be responsible for maintaining the blind, consistent with protocol design, throughout the study. All documentation is to be filed in the Pharmacy Manual. Access to this manual by study personnel will be restricted to the unblinded pharmacy staff.

The subjects, Principal Investigator, and all other study personnel involved with subject assessments will remain blinded to the actual treatment assignments of the subjects. The Principal Investigator will be ultimately responsible for ensuring that the integrity of the blind is maintained throughout the study, and will be required to notify the Sponsor in the event of any breaking of the blind for any reason.

6.2.1 Clinical Research Staff

All observers who evaluate any reported adverse event, laboratory abnormalities, ECGs, and changes in the ECGs will be blinded as to what treatment sequence each subject is assigned.

6.2.2 Study Subjects

All subjects will be blinded as to which treatment they are receiving at any dose.

6.2.3 Bioanalytical Laboratory

All samples will be sent to the bioanalytical laboratory for analysis. The bioanalytical laboratory will be unblinded and only run the analysis on active treatment subjects.

6.2.4 Pharmacokinetic Analysis

Pharmacokinetic analysis will be completed only on the active treatment subjects and will be blinded by subject for interim assessments.

6.2.5 Unblinding Procedures

As data from each cohort is informative for dose escalation decisions in subsequent cohorts, review of unblinded data will be conducted after completion of each cohort by 2 experienced individuals not directly involved in the study, one of whom must be a physician. Per protocol, the dose escalation meeting and decision require PK data through the morning of Day 15 and approximately 21 days of safety data, depending on the turnaround time of the bioanalysis. Upon completion of the review, they will communicate to the study team modifications, if any, that should be implemented for subsequent cohorts.

The treatment assignment should be unblinded at the clinic only in the case of an emergency, when knowledge of the study drug assignment is absolutely necessary for the clinical management or welfare of the subject. Breaking of the blind at the clinic under any other circumstances will be considered a protocol violation.

The Investigator is strongly encouraged to contact the Sponsor before unblinding the study drug assignment prior to the scheduled assessment of tolerance and safety data. If the blind is broken for any reason, the Investigator must notify the Sponsor within

1 day, and an SAE form must be completed, if appropriate. In addition, the Investigator will record the date and reason for revealing the blinded study drug assignment for that subject in the source documents and appropriate CRF page(s).

6.3 Check-In Procedures

Subjects will check into the clinic on Day -2.

At check-in, all subjects will be evaluated to confirm they continue to meet all the inclusion criteria (Section 5.1) and none of the exclusion criteria (Section 5.2). Subjects will undergo the following assessments during the confinement period prior to dosing:

- Physical and neurological examinations
- Vital signs (temperature, respirations, blood pressure, pulse, and pulse oximetry)
- Triplicate 12-lead ECG
- Urine drug, alcohol, and cotinine screens – results must be negative for the subject to continue study participation
- Serum pregnancy test (all female subjects) – results must be negative for the subject to continue study participation
- Concomitant medication review
- AE review

6.4 Confinement

Subjects will be admitted to the research center on Day -2.

Subjects in the food-effect cohorts will remain confined until after completion of the Day 20 procedures and will return for follow-up outpatient visits on Days 21-26. Subjects will receive a follow up phone call on Day 33 (+1 day).

Subjects in the non-food-effect cohort will remain confined until after completion of the Day 17 procedures and will return for follow-up outpatient visits on Days 18-23. Subjects will receive a follow up phone call on Day 30 (+1 day).

6.5 Fasting/Meals/Beverages

6.5.1 Fasting/Meals

An optional meal may be served the evening of check-in.

All subjects in the food-effect cohorts will be required to fast for at least 10 hours before the first dose on Day 1. The subjects will fast for 4 hours thereafter.

For Days 4-17 in the food-effect cohorts and Days 1-14 for the non-food-effect cohort, all subjects will then be required to fast for at least 10 hours before consuming a required FDA standard high-fat, high-calorie breakfast. Subjects will receive the required FDA standard high-fat, high-calorie breakfast to begin 30 minutes before

scheduled administration of the dose and to end (last bite taken) within 5 minutes before dosing. The subjects will fast for 4 hours thereafter. An FDA standard high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 1000 calories) breakfast consists of:

2 eggs fried in butter
2 strips of bacon
2 slices of toast with butter
4 ounces of hash brown potatoes
8 ounces of whole milk

This meal contains approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories. An equivalent meal may be substituted with documentation of the menu and caloric contents.

Standard meals will be provided at approximately 4 and 10 hours after drug administration and at appropriate times thereafter.

6.5.2 Beverages

Except for 200 mL of the room temperature water provided with the study treatment, no water may be consumed for 1 hour prior to each dose through 1 hour after each dose.

At other times, subjects will be encouraged to drink water ad libitum.

6.6 Drug Administration

6.6.1 Administration of TBI-223 Sustained Release and Immediate Release Tablets or Placebo Tablets for TBI-223

Each subject will receive the oral dose of the assigned study treatment with approximately 200 mL of room temperature water. Subjects must swallow the study medication intact. The medication should NOT be crushed or chewed. A hand and mouth check will be performed immediately after dose to ensure that the medication has been appropriately swallowed.

The subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after dosing. Should the need to move about occur during the first 4 hours after each dose, subjects may be escorted to such procedures or activities by research personnel as deemed medically necessary. Subjects will not be allowed to lie down, except as directed by clinical staff secondary to AEs, for the first 4 hours after dosing.

6.7 Blood Sampling, Processing and Shipment

Blood samples will be collected as detailed in Appendix 1.

Refer to the Schedule of Events for specific blood collection time points. The Principal Investigator, in conjunction with the Sponsor, may collect additional blood if necessary for repeat laboratory or safety evaluations including AE follow-up.

After Day -1, blood for clinical labs and coagulation testing should be collected 6-7 hours postdose.

For the food-effect cohorts, a total of 60 mL (15 x 4 mL samples) will be collected from each subject for plasma predose trough pharmacokinetic analysis. A total of 204 mL (51 x 4 mL samples) will be collected from each subject for plasma postdose pharmacokinetic analysis. Approximately 144.2 mL of blood will be collected for the clinical laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately 408.2 mL.

Table 6 Total Volume of Blood to be Collected for Testing, Food-Effect Cohorts

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	12.5	12.5
Clinical labs during study (Days -1, 1, 2, 3, 4, 5, 6, 10, 14, 17, 20 and 26/end-of-study)	12	8.5	102
Coagulation (screening and Days -1, 1, 3, 4, 6, 10, 14, 17, 20, and 26)	11	2.7	29.7
Pharmacokinetic analysis (predose, trough)	15	4.0	60.0
Pharmacokinetic analysis (postdose)	51	4.0	204.0
		Total	408.2

For the non-food-effect cohort, a total of 56 mL (14 x 4 mL samples) will be collected from each subject for plasma predose trough pharmacokinetic analysis. A total of 208 mL (52 x 4 mL samples) will be collected from each subject for plasma postdose pharmacokinetic analysis. Approximately 90.9 mL of blood will be collected for the clinical laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately 274.9 mL.

Table 7 Total Volume of Blood to be Collected for Testing, Non-Food-Effect Cohort

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	12.5	12.5
Clinical labs during study (Days -1, 1, 3, 6, 10, 14, and 23/end-of-study)	7	8.5	59.5
Coagulation (screening and Days -1, 1, 6, 10, 14, and 23)	7	2.7	18.9
Pharmacokinetic analysis (predose, trough)	14	4.0	56.0
Pharmacokinetic analysis (postdose)	32	4.0	128
		Total	274.9

The Principal Investigator, in conjunction with the Sponsor, may collect additional blood if necessary for repeat laboratory or safety evaluations including AE follow-up.

6.7.1 Pharmacokinetic Sampling Time Windows

Blood samples collected within the time windows listed below will not be considered deviations. Note: The 24-hour sample of Day 1 must be collected prior to the Day 2 dose.

Table 8 Acceptable Pharmacokinetic Sampling Time Windows, Food-Effect Cohorts

Investigation and examination	Allowable Time Window		
	Postdose		
	≤24 hours	>24 hours to ≤Day 20	>Day 20
Plasma sample collection for pharmacokinetic assessment	± 2 minutes[a]	± 5 minutes	± 10 minutes
a: The 24-hour sample of Day 1 must be collected prior to the Day 2 dose; the 2-minute window does not apply.			

Table 9 Acceptable Pharmacokinetic Sampling Time Windows, Non-Food-Effect Cohort

Investigation and examination	Allowable Time Window		
	Postdose		
	≤24 hours	>24 hours to ≤Day 17	>Day 17
Plasma sample collection for pharmacokinetic assessment	± 2 minutes[a]	± 5 minutes	± 10 minutes
a: The 24-hour sample of Day 1 must be collected prior to the Day 2 dose; the 2-minute window does not apply.			

6.8 End-of-Study Procedures

On the day of study discharge (Day 23 for non-food-effect cohort and Day 26 for the food-effect cohorts), the following procedures will be conducted:

- Physical and neurological examinations
- Vital signs measurements (blood pressure, pulse, temperature, respirations, and pulse oximetry)
- Clinical laboratory tests (hematology, chemistry, urinalysis)
- Coagulation
- Triplicate 12-lead ECG
- Concomitant medication review
- AE assessment

Subjects will receive a follow up phone call on Day 30 (non-food-effect cohort) or Day 33 (food-effect cohorts) (+1 day).

6.9 Safety Monitoring and Procedures

6.9.1 Adverse Events

Subjects will be instructed to inform the study physician and/or research personnel of any AEs that occur at any time during the study. Subjects will be monitored for AEs from the first dose through the end-of-study visit.

Refer to Section 7 for details regarding AE reporting.

6.9.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at the times noted on the events schedule (Table 6 for food-effect cohorts and Table 7 for non-food-effect cohort). A Clinical Laboratory Improvement Amendments (CLIA) certified laboratory will perform all clinical laboratory tests for this study. If exclusionary lab criteria are met, values may be confirmed by repeat evaluation.

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell count (RBC), and platelet count.
- Serum Chemistry: albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na+), potassium (K+), chloride (Cl-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, glucose, gamma-glutamyltransferase (GGT), and magnesium.
- Serology: hepatitis B surface antigen, hepatitis C antibody, and HIV.
- Coagulation: prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- Urinalysis - The following will be evaluated by an automated or manual urine "dipstick" method: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen. If protein, occult blood, nitrite, or leukocyte esterase values are out of range, a microscopic examination will be performed.
- Urine Drug, Cotinine, and Alcohol Screens: drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates), alcohol, and cotinine.
- Pregnancy test (all female subjects).
- Follicle-stimulating hormone (female subjects claiming post-menopausal status).

6.9.3 Vital Signs

Vital signs (blood pressure, pulse rate, and respiration rate, pulse oximetry, and temperature) will be measured performed at the times noted on the events schedule (Table 6 for food-effect cohorts and Table 7 for non-food-effect cohort).

NOTE: Blood pressure and pulse rate will be captured simultaneously. Blood pressure and pulse rate should be measured after subjects are in a seated position for 2 minutes and then again after standing for 1 minute, except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.

For purposes of qualifying any given subject for study participation, out-of-range vital signs may be repeated once.

Predose vital signs will be assessed by the Principal Investigator or designee (e.g., a medically qualified Sub-Investigator) prior to each study drug administration. The Principal Investigator or designee will verify the eligibility of each subject with out-of-range vital signs and document approval prior to dosing.

Additional vital signs measurements may be performed as deemed medically necessary by research personnel.

6.9.4 Physical Examinations

Physical examinations, including height and weight measurements, will be conducted at the times noted on the events schedule (Table 6 for food-effect cohorts and Table 7 for non-food-effect cohort).

6.9.5 Neurological Examinations

Detailed neurological examinations will be conducted at the times noted on the events schedule (Table 6 for food-effect cohorts and Table 7 for non-food-effect cohort) and at unscheduled time points as deemed necessary by the Investigator. Each neurological exam will assess the following:

- Mental Status – orientation, speech, and memory
- Cranial Nerves – excluding fundoscopic examination
- Muscle tone and strength
- Sensory System – brief survey for light touch and temperature of the face, neck, arms, trunk, and legs
- Reflexes –deep tendon reflexes and plantar responses (Babinski sign)
- Coordination – upper and lower extremities, including tremor
- Gait – tandem gait

6.9.6 12-Lead Electrocardiograms

Safety 12-lead ECGs will be recorded and printed for on-site review by the Principal Investigator or designee at the times noted on the events schedule (Table 6 for food-effect cohorts and Table 7 for non-food-effect cohort).

The predose ECG should be completed within 20 minutes prior to the predose blood draw.

All safety ECGs will be performed after the subject has been in supine position for a minimum of 5 minutes.

If a subject experiences a post-dosing QTcF >500 msec or a change-from-baseline QTcF ≥60 msec, after repeat testing, additional ECGs should be recorded until normalization or return to baseline.

6.9.7 Other Safety Measures

Medical emergency personnel trained in advanced cardiac life support will be on site to monitor subjects during the confinement period in the research center. Emergency

medical equipment including but not limited to intubation equipment and pulse oximetry shall be maintained on site to administer appropriate medical care should it be required.

Procedures will be completed as specified in this protocol unless contraindicated due to a reported AE.

7 ADVERSE EVENTS

The Investigator or a suitably medically qualified designee are responsible for eliciting adverse events by observing and questioning the subject and recording all adverse events observed by him/her or reported by the subject during the trial.

7.1 Definitions

7.1.1 Adverse Event

Any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a trial treatment whether or not considered related to trial treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a trial treatment, whether or not related to the trial treatment.

7.1.2 Serious Adverse Event

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; In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE;
- Results in persistent or significant disability/incapacity; the term disability means a substantial disruption of a person's ability to conduct normal life functions. This

definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption;

- Is a congenital anomaly/birth defect; or
- Is a medically important event.

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the 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".

7.2 Attribution/Causality

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).

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor/designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/designee.

- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

Table 10 Adverse Event 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).

Table 11 Definitions for Adverse Event Severity Gradings

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.

See Appendix 3 for full DMID Toxicity Tables. The above ratings should be used to estimate the grade for abnormalities NOT found elsewhere in the Toxicity Tables. Lab results within the testing facility's normal range will not be considered AEs when referenced to the DMID assessment/grading scale (Appendix 3).

Laboratory abnormalities and cardiovascular findings of hypertension or hypotension Grade 2 or above on the DMID toxicity tables will be considered AEs.

7.3 Reporting

7.3.1 Adverse Event

Adverse Events will be collected by the Investigator or qualified designee(s) from the time a subject signs the Informed Consent Form through the follow-up phone calls (Day 14 for the Single Ascending Dose Cohort and Day 28 for the Multiple Ascending Dose Cohorts).

Any AE (serious or non-serious) observed by the Investigator (or a suitably medically qualified designee) or reported by the subject will be recorded on the Adverse Event Case Report Form. The Investigator will review each AE and assess its relationship to drug treatment based on all available information at the time of the completion of the CRF. The following information will be recorded for each Adverse Event reported:

- 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 (with duration, if applicable);
- Severity;
- Action taken with IMP;
- Other action taken;
- Outcome;
- Relationship to IMP;
- Occurrence;
- Seriousness

7.4 Serious Adverse Event Reporting

The Investigator or designee will notify the appropriate Sponsor contact immediately after the SAE detection, observation, or report of occurrence (regardless of the relationship to test article). The Sponsor contact information for SAE reporting is provided below:

TB Alliance Pharmacovigilance
Email: AE_inbox@tballiance.org

Questions relative to SAE processing may also be sent to the above mentioned email address. If there is ever any email failure upon trying to report an SAE, please call Dr. Bruinenberg at +1.201.312.0988 and he will notify the safety team at TB Alliance.

Medical questions relative to AEs and SAEs can be directed to:

Paul Bruinenberg MD, MBA
Global Alliance for TB Drug Development
40 Wall Street, 24th Floor
New York, NY 10005, United States of America
Telephone: +1 646.616.8629
Mobile: +1 201.312.0988
Facsimile: +1 212.227.7541
Email: Paul.Bruinenberg@tballiance.org

These SAE reports must contain the following information:

A. Study name/number (for EU also the Eudract number)
B. Study drug
C. Investigator details (name, phone, fax, e-mail)
D. Subject number
E. Subject demographics
F. Clinical event:
    1) Description
    2) Date of onset
    3) Treatment (drug, dose, dosage form)
    4) Adverse event relationship to study drug
    5) Action taken regarding study drug in direct relationship to the AE
G. If the AE was fatal or life-threatening
H. If applicable, cause of death (whether or not the death was related to study drug)
I. If applicable, autopsy findings (if available)

Any new SAE that occurs within one month after the study period and is considered to be possibly related to the Investigational Product (IP) should be recorded and reported immediately to the Sponsor.

The person responsible for the study shall take care that the study has been carried out in accordance with pharmacovigilance local regulations.

All serious event reporting will adhere to U.S. Code of Federal Regulations (21 CFR Part 312.32) for IND drugs and 21 CFR 314.80 for marketed drugs (15-day alerts). The Institutional Review Board (IRB) will be notified of the alert reports per Food and Drug Administration (FDA) regulations.

All AEs, including SAEs, will be followed to resolution when possible. All AEs and treatment administered will be recorded on the case report form (CRF).

The Sponsor will be responsible for processing and reporting any SAEs (and their relevant updates) to the FDA or other applicable regulatory agency.

7.5 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- End of the follow-up period; and
- All queries on these AEs have been resolved.

Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In these cases, follow-up will be the responsibility of the treating physician. However, this will have to be agreed upon with the Sponsor Medical Monitor.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. Investigator should contact sponsor/designee to discuss appropriate medical follow-up if consultation required.

If a participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide sponsor/representative with a copy of any post-mortem findings including histopathology.

New or updated information on an SAE will be recorded in the originally completed CRF and submitted to sponsor within 24 hours of the information becoming known per SAE reporting guidelines.

7.6 Post-Trial Serious Adverse Events

Any new SAEs reported by the subject to the Investigator that occur up to 30 days after last contact, and are determined by the Principal Investigator to be possible, probable or very likely related to the use of the IMP, will be reported to the Sponsor, IRB and FDA on an expedited basis as required in accordance with local requirements and ICH guidelines for GCP.

7.7 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.

7.8 Drug Interaction

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

7.9 Pregnancy

The Investigator will immediately notify the Sponsor of any pregnancy that is discovered during the clinical trial. Pregnancy forms will be completed for all pregnancies reported during the study or in the 30 days after completion of the IMP. In addition, the Investigator will report to the Sponsor follow up information regarding the outcome of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for 6 months.

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

If the Investigator becomes aware the female partner of a male subject becomes pregnant during the study or in the 30 days after the completion of IMP, consent will be requested from the female partner for collection of information on her pregnancy history and for information on the current pregnancy and birth.

7.10 Monitoring and Safety for Specific Toxicities

During preclinical testing, issues with increased heart rate and lowering of blood pressure were detected. Therefore, heart rate and blood pressure changes should be monitored carefully. When abnormalities are detected both blood pressure and pulse rate should be captured simultaneously

8 GENERAL CONSIDERATIONS

8.1 Basic Principles

This research will be carried out in accordance with the protocol, the International Council for Harmonisation (ICH), Guideline for Good Clinical Practice: Consolidated Guidance (E6), and applicable regulatory requirements(s) including clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Parts 50, 56, and 312 and the principles enunciated in the Declaration of Helsinki (revised version Fortaleza 2013).

8.2 Institutional Review Board

This protocol will be reviewed by an appropriate IRB and study enrollment will not commence until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in 21 CFR Part 56.

8.3 Informed Consent

Written informed consent will be obtained from each subject prior to performing any baseline study-specific evaluations. The informed consent document is prepared by the Investigator or designee, subject to review and approval by the Sponsor, and forwarded to a qualified IRB for final review and approval. The IRB-approved document must contain, at minimum, the eight basic elements of informed consent. Only the most recently IRB-approved Informed Consent Document must be used to consent prospective study subjects. One copy of the signed and dated informed consent document will be given to the subject and the original retained by the Investigator/site.

8.4 Indications for Subject Withdrawal

Subjects will be free to withdraw at any time for any reason, or they may be withdrawn if necessary, to protect their health and safety or the integrity of the study data.

The final report will include reasons for withdrawals. In the event of an early termination, subjects will undergo the procedures described in Section 6.8.

Subjects who experience emesis may be replaced if the emesis could potentially impact drug absorption and therefore the pharmacokinetic data. Cases of emesis will be evaluated by the Sponsor and Principal Investigator to determine if subject replacement is needed.

8.5 Termination of the Study

The Principal Investigator reserves the right to terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to terminate the study at any time for administrative reasons.

8.6 Documentation

All documents pertaining to the study, including a copy of the approved protocol, copy of the informed consent document and Health Insurance Portability and Accountability Act (HIPAA) documents, completed CRFs (where applicable), drug accountability and retention records, and other study related documents will be retained in the permanent archives of the study site. These will be available for inspection at any time by the Sponsor or the FDA. Per 21 CFR 312, record retention for this study is required for a period of two years following the date on which this study agent is approved by the FDA for the marketing purposes that were the subject of this investigation; or, if no application is to be filed or if the application is not approved for such indication, until two years following the date on which the entire study is completed, terminated, or discontinued, and the FDA is notified.

Subject records will be kept private except when ordered by law. The following individuals will have access to study subject records: Principal Investigator and designees, study Sponsor, monitors, and auditors, the FDA, other government offices, and the IRB.

8.7 Trial Monitoring

Sponsor personnel (or designees) will be responsible for monitoring the study to ensure compliance with the protocol and GCP. Compliance may be verified by one or more of the following methods: on-site visits, frequent communication with the Investigator, and/or review of CRFs and source documents. The Investigator agrees to permit such monitoring as well as audits or reviews by regulatory authorities and the IRB.

8.8 Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

9 PHARMACOKINETIC ANALYSIS

9.1 Analytical Methodology

Plasma samples will be analyzed for TBI-223 and M2 using validated assays. Plasma samples from subjects who receive placebo for TBI-223 will not be analyzed.

9.2 Pharmacokinetic Analysis

Pharmacokinetic calculations will be performed using appropriate software, e.g. Phoenix™ WinNonlin® (Version 8.1 or higher, Pharsight Corporation) and/or SAS® (Version 9.4 or higher, SAS Institute Inc.).

Pharmacokinetic parameters will be calculated using non-compartmental analysis. The following pharmacokinetic parameters will be determined as appropriate as detailed below.

AUC_{Extrap} (%)	The percentage of AUC_{inf} based on extrapolation
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity; calculated as: $AUC_{inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$
AUC_{last}	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{tau}	Area under the concentration-time curve during the dosing interval
C_{avg}	Average steady-state concentration
C_{last}	The last quantifiable concentration determined directly from individual concentration-time data
CL/F	Apparent total clearance after single administration
CLs/F	Apparent total clearance at steady state
C_{min}	Minimum concentration
C_{max}	Maximum concentration, determined directly from individual concentration-time data
C_{trough}	Trough plasma concentration
R_{AUC}	Accumulation ratio for AUC
R_{Cmax}	Accumulation ratio for C_{max}
T_{last}	Time of the last quantifiable concentration
T_{max}	Time of the maximum concentration
$T_{1/2}$	The observed terminal half-life, calculated as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$

Vz/F	Apparent volume of distribution in the terminal phase
λ_z	The observed terminal rate constant; estimated by linear regression through at least three data points in the terminal phase of the log concentration-time profile

For the non-food-effect cohorts, PK parameters calculated from plasma concentration of TBI-223 and M2 following doses on Days 1 and 14 will include, as appropriate:

- Day 1: AUC_{tau}, C_{max}, C_{24}, C_{avg}, $T_{max.}$ Additionally, AUC_{inf}, AUC_{extrap}, CL/F, V_z/F, λz, and $t_{1/2}$ should be included if $AUC_{tau} \geq 70\%$ of $AUC_{inf.}$
- Day 14: $AUC_{tau,}$ $C_{max,}$ C_{min}, C_{trough} (i.e., C_0), C_{24}, $C_{avg,}$ T_{max}, CL/F, V_z/F, λz, $t_{1/2}$, R_{AUC}, R_{Cmax}

For the food-effect cohorts, PK parameters calculated from plasma concentration of TBI-223 and M2 following doses on Days 1, 4, and 17 will include, as appropriate:

- Day 1: AUC_{tau}, AUC_{extrap}, $AUC_{inf,}$ C_{max}, C_{24}, C_{last}, T_{max}, T_{last}, CL/F, V_z/F, λz, $t_{1/2.}$
- Day 4: AUC_{tau}, C_{max}, C_{24}, $C_{avg,}$ T_{max}. Additionally, AUC_{inf}, AUC_{extrap}, CL/F, V_z/F, λz, $t_{1/2}$ should be included if $AUC_{tau} \geq 70\%$ of $AUC_{inf.}$
- Day 17: $AUC_{tau,}$ $C_{max,}$ C_{min}, C_{trough} (i.e., C_0), C_{24}, $C_{avg,}$ $T_{max,}$ CL/F, V_z/F, λz, $t_{1/2}$, R_{AUC}, R_{Cmax}

Each parameter will be estimated separately for each participant using plasma concentrations of TBI-223 and, as appropriate M2.

Each day one blood sample will be taken immediately before dosing, to measure C_{trough} level and to observe the time that steady state is achieved.

Assessments of food effect will include geometric mean ratios of C_{max} and AUC_{tau} between Day 1 (fasted) and Day 4 (fed), as well as graphical displays of the profiles. Model-based approaches and comparisons with results from the single-dose study, TBI-223-CL-001, may also be undertaken.

Both individual-participant and group summary-statistics (n, mean, median, geometric mean, standard deviation, standard error of the mean, coefficient of variation, minimum, maximum) data will be reported. Summary statistics will be presented by gender. All tests will be performed using a 2-sided α-level of 0.05, and appropriate confidence intervals will be provided.

9.3 Statistical Analysis

Statistical analyses will be performed using appropriate software, e.g. Phoenix™ WinNonlin® (Version 8.1 or higher, Pharsight Corporation) and SAS® (Version 9.4 or higher, SAS Institute Inc.).

Pharmacokinetic parameters will be summarized by cohort using descriptive statistics. Summary statistics will also be presented by gender within each cohort.

Dose proportionality will be assessed using a power model approach.

10 FACILITIES

CLINICAL TRIAL SITE

TKL Research, Inc.
One Promenade Blvd. Suites 1101 & 1201
Fair Lawn, New Jersey 07410
Telephone: 201.587.0500

CLINICAL LABORATORIES

Quest Diagnostics
One Malcolm Avenue
Teterboro, New Jersey 07608
Telephone: 888.604.5770
Fax: 551.256.8833

ANALYTICAL LABORATORY

Alliance Pharma, Inc.
Project Manager: Duxi Zhang
Contact for Sample Shipment: Ruth Guan
17 Lee Boulevard
Malvern, PA 19355
Phone: 610.296.3152
Fax: 610.296.3153
Email: dzang@alliancepharmaco.com; samples@alliancepharmaco.com
Web: www.alliancepharmaco.com

11 DRUG SUPPLIES

Global Alliance for TB Drug Development will supply sufficient a quantity of the study drug, TBI-223 SR1 tablets, TBI-223 IR tablets, and Placebo for TBI-223 IR and SR1 tablets 600 mg. Study drug will be shipped to TKL Research, Inc. pursuant to site standard operating procedures. Upon receipt of the study drug products, the supplies will be inventoried and stored in an environmentally controlled and secure, limited access area. The lot numbers of the drugs along with the expiration dates (where available) will be recorded and copies of the Certificate of Analysis (where available) will be maintained on file. Records will be maintained of the receipt and dispensation of the drugs supplied. At the conclusion of the study, any unused study drug will be

returned to the sponsor or destroyed by the site pursuant to written authorization by the sponsor and applicable federal and state regulations.

12 ADMINISTRATIVE ISSUES

The Investigator is referred to the Investigator Brochure, or information provided during the study initiation visit, information provided by the study monitor, and ICH Guidelines for Good Clinical Practice for information regarding the study drug, details, or general considerations to be followed during the course of this study.

13 EVENTS SCHEDULE

Table 12 Schedule of Assessments (Cohorts 1 and 2)

	SCREEN	CHECK-IN[a]	Fasted dosing Day 1 and washout Day 2-3				TREATMENT (14 Days) Day 18-19 Follow-up					CHECK OUT	FOLLOW-UP			EARLY WITHDRAWAL
DAY	-28 to -2	-2	-1	1	2	3	4	5-10	11	12-17	18-19	20	21-25	26	33 (+1)	
EVENT																
Informed consent and medical history	X															
Check-in questions		X														
Height, weight	X															
HIV/ hepatitis B, C	X															
Serum pregnancy test[b]	X	X														
FSH[b]	X															
Urine drug/alcohol/cotinine screen	X	X														
Safety Labs (hematology, chemistry)[c]	X		X	X	X	X	X	X[c]		X[c]		X		X		X
Coagulation[d]	X		X	X		X	X	X[d]		X[d]		X		X		X
Urinalysis[e]	X		X	X		X	X	X[e]		X[e]		X		X		
Physical and neurological exams[f]	X	X	X	X	X	X	X	X[f]		X[f]				X		X
Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry)[g]	X	X		X	X	X	X	X	X	X	X	X	X	X		X
Concomitant medication review[h]		←----------X----------→														
Adverse events[i]		←----------X----------→														

	SCREEN	CHECK-IN[a]	Fasted dosing Day 1 and washout Day 2-3				TREATMENT (14 Days) Day 18-19 Follow-up					CHECK OUT	FOLLOW-UP			EARLY WITHDRAWAL
DAY	-28 to -2	-2	-1	1	2	3	4	5-10	11	12-17	18-19	20	21-25	26	33 (+1)	
EVENT																
Dose[j]				X			X	X	X	X						
12-lead safety ECGs[k]	X	X	X	X			X	X		X	X	X		X		X
Plasma for predose trough PK[l, m]				X			X	X	X	X						
Plasma for Postdose PK[n]				X	X	X	X			X	X	X				

ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; PK = pharmacokinetic.

a. Confinement to start at Check-in (evening of Day -2) and continue until 72 hours after dosing on Day 17.
b. Serum pregnancy test at screening and at check-in for females only. FSH completed for postmenopausal females only.
c. Blood will be collected for safety labs (hematology and chemistry) at Screening and Day -1 and at 6-7 hours postdose on Days 1, 2, 3, 4, 6, 10, 14, 17, and on Days 20 and 26
d. Blood for coagulation testing will be collected at Screening and Day -1, and 6-7 hours postdose on Days 1, 3, 4, 6, 10, 14, 17, and on Days 20 and 26.
e. Urinalysis testing at Screening and Days -1, 1, 3, 4, 6, 10, 14, 17, and on Days 20 and 26.
f. Neurological exam: Performed at Screening, Day -2 and Day -1 around 6-7 hours postdose and prior to blood collection for safety labs on Days 1, 4, 6, 10, 14, 17, and on Day 26.
g. Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate) should be measured at screening, check-in, and while subjects are in confinement. Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the remaining defined time points in flowchart at study hours 0, 1, 6, and 12 on Days 1 and 17. Furthermore, vital signs will be taken once daily on Days 1 through Day 20 (6 hours after dosing) and once daily on Days 18 through 26 and at early withdrawal (must be done within 15 minutes before review of medication and collection of adverse experiences). Both blood pressure and heart rate should be captured simultaneously. Blood pressure and heart rate should be measured after subjects are in a seated position for 2 minutes and again after standing for 1 minute, except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.
h. On Day 33 (+1 day), follow-up questioning on concomitant medications will be completed by a phone call.
i. Subjects will be monitored for treatment-emergent adverse events to be monitored from the time of dosing and throughout the study via safety assessments, observation and participant reporting. Specific adverse event questions will be posed daily throughout the study until Day 26. The inquiry to collect adverse events using non-leading questions will be performed after all other procedures are conducted for the specified time points. On Day 33 (±1 day), follow-up questioning on adverse events will be completed by a phone call.
j. TBI-223 SR1 and IR tablets and placebo for TBI-223 will be administered orally followed by approximately 200 mL of water. **Note:** Dosing on Day 1 will be fasted. Dosing on Days 4-17 to occur following a high-fat, high-calorie breakfast to begin 30 minutes prior to dose and to end (last bite taken) within 5 minutes prior to dosing
k. 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Triplicate ECGs will be completed at screening, Day -2, Day -1, and on Day 26 or upon early withdrawal. All other time points will be single ECG readings. ECGs may be done within 2 hours prior

to time of dosing and at 3, 6, 12 and 16 hours postdose on Days 1, 4, 8, 10, 12, 14, 17, and on Days 18 and 20. Another single ECG reading will be performed on the morning of Day 20 before discharge. The predose ECG should be completed within 20 minutes prior to the predose blood draw. If a subject experiences a post-dosing QTcF >500 msec with a change-from-baseline QTcF >60 msec, after repeat testing, additional ECGs should be recorded until normalization or return to baseline

l. Predose trough blood samples will be drawn on Day 1 and daily starting on Day 4.
m. Duplicate plasma samples will be generated from all blood pharmacokinetic samples.
n. Postdose blood plasma samples will be drawn at the following timepoints:
   - Day 1: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, and 72 hours. The 72-hour sample is the predose sample of Day 4.
   - Day 4: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, and 24 hours. The 24-hour sample is the predose sample of Day 5.
   - Day 17: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, and 72 hours

Table 13 Schedule of Assessments (Cohort 3)

	SCREEN	CHECK-IN[a]		TREATMENT						CHECK OUT	FOLLOW-UP			EARLY WITHDRAWAL
DAY	-28 to -2	-2	-1	1	2 - 6	7	8-13	14	15-16	17	18-22	23	30 (+1)	
EVENT														
Informed consent and medical history	X													
Check-in questions		X												
Height, weight	X													
HIV/ hepatitis B, C	X													
Serum pregnancy test[b]	X	X												
FSH[b]	X													
Urine drug/alcohol/cotinine screen	X	X												
Safety Labs (hematology, chemistry)[c]	X		X	X	X[c]		X[c]	X				X		X
Coagulation[d]	X		X	X	X[d]		X[d]	X				X		X
Urinalysis[e]	X		X	X	X[e]		X[e]	X				X		
Physical and neurological exams[f]	X	X	X	X	X[f]		Xf	X				X		X
Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry)[g]	X	X		X	X	X	X	X	X	X	X	X		X
Concomitant medication review[h]		←----------X----------→												
Adverse events[i]				←----------X----------→										
Dose[j]				X	X	X	X	X						
12-lead safety ECGs[k]	X	X	X	X	X		X			X		X		X
Plasma for predose trough PK[l, m]				X	X	X	X	X						
Plasma for Postdose PK[n]				X				X	X	X				

ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; PK = pharmacokinetic.

a. Confinement to start at Check-in (evening of Day -2) and continue until 24 hours after dosing on Day 14.
b. Serum pregnancy test at screening and at check-in for females only. FSH completed for postmenopausal females only.
c. Blood will be collected for safety labs (hematology and chemistry) at Screening and Day -1 and at 6-7 hours postdose on Days 1, 3, 6, 10, 14, and on Day 23.
d. Blood for coagulation testing will be collected at Screening and Day -1, and 6-7 hours postdose on Days 1, 6, 10, 14, and on Day 23.
e. Urinalysis testing at Screening and Days -1, 1, 6, 10, 14, and 23.
f. Neurological exam: Performed at Screening, Day -2 and Day -1 and 6-7 hours postdose and prior to blood collection for safety labs on Days 1, 3, 6, 10, 14, and on Day 23.
g. Vital signs (blood pressure, heart rate [pulse], temperature, and respiration rate) should be measured at screening, check-in, and while subjects are in confinement. Vital sign measurements should be taken within 90 minutes prior to dosing and within 15 minutes of the remaining defined time points in flowchart at study hours 0, 1, 6, and 12 on Days 1 and 14. Furthermore, vital signs will be taken once daily on Day 2 through Day 14 (6 hours after dosing) and once daily on Days 15 through 23 and at early withdrawal (must be done within 15 minutes before review of medication and collection of adverse experiences). Both blood pressure and heart rate should be captured simultaneously. Blood pressure and heart rate should be measured after subjects are in a seated position for 2 minutes and then again after standing for 1 minute, except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.
h. On Day 30 (+1 day), follow-up questioning on concomitant medications will be completed by a phone call.
i. Subjects will be monitored for treatment-emergent adverse events to be monitored from the time of dosing and throughout the study via safety assessments, observation and participant reporting. Specific adverse event questions will be posed daily throughout the study until Day 23. The inquiry to collect adverse events using non-leading questions will be performed after all other procedures are conducted for the specified time points. On Day 30 (±1 day), follow-up questioning on adverse events will be completed by a phone call.
j. TBI-223 SR1 and IR1 tablets and placebo for TBI-223 will be administered orally followed by approximately 200 mL of water. **Note:** Dosing to occur following a high-fat, high-calorie breakfast to begin 30 minutes prior to dose and to end (last bite taken) within 5 minutes prior to dosing
k. 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Triplicate ECGs will be completed at screening, Day -2, Day -1, and on Day 23 or upon early withdrawal. All other time points will be single ECG readings. ECGs may be done within 2 hours prior to time of dosing and at 3, 6, 12, and 16 hours postdose on Days 1, 2, 3, 8, 12. Another single ECG reading will be performed on the morning of Day 17 before discharge. The predose ECG should be completed within 20 minutes prior to the pre-dose blood draw. If a subject experiences a post-dosing QTcF >500 msec with a change-from-baseline QTcF >60 msec, after repeat testing, additional ECGs should be recorded until normalization or return to baseline
l. Predose trough blood samples will be drawn daily starting on Day 1.
m. Duplicate plasma samples will be generated from all blood pharmacokinetic samples.
n. Postdose blood plasma samples will be drawn at the following timepoints:
    - Day 1: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, and 24 hours. The 24-hour sample is the predose sample of Day 2.
    - Day 14-17: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, and 72 hours

14 REFERENCES

1. Investigator's Brochure for TBI-223
2. Prescription Monograph for Linezolid
3. FDA Guidance for Industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

APPENDIX 1 PHARMACOKINETIC SAMPLE PROCESSING

A. Collection and Processing

A more detailed description of plasma sample preparation requirements may be provided by the analytical laboratory. If such a description is provided, the method of sample preparation provided by the laboratory shall supersede those provided in this protocol and appropriate documentation shall be placed in the Investigator Site File (ISF).

Processing Instructions	
1	Samples will be collected via direct venipuncture at the time points delineated in the appropriate Events Schedule (Section 13).
2	Blood will be drawn into pre-chilled 4 mL evacuated tubes containing K_3-EDTA and immediately placed on wet ice and then processed to plasma within 60 minutes.
3	Samples will be centrifuged at 1500 g at approximately 4°C (± 10 degrees) for 10 minutes. After centrifugation, two aliquots of plasma (the first containing at least 0.5 mL and the second containing the remainder of the plasma) will be removed and placed in appropriately labeled 5 mL polypropylene vials.
4	The aliquots will be immediately placed on dry ice. Within 90 minutes of collection, the aliquots will be stored in a freezer set at -20°C ± 10°C and remain in the freezer until transferred for analysis.
5	Samples will be transferred at the agreed upon intervals.
6	The aliquots will be transferred on dry ice to the Alliance Pharma, Inc. bioanalytical laboratory for the determination of plasma concentrations of TBI-223 and TBI-223-M2, using a validated procedure at Alliance Pharma.
7	Blood sampling, plasma processing, and storage time will be documented in the study records.

Labeling of aliquot tubes

Labels will contain at least the following information:

a) Study number

b) Subject number

c) Period or dosing phase; sampling time (relative to dosing)

d) Aliquot letter (A or B)

Shipment

1. The samples will be transferred to the analytical laboratory after completion of the study or at mutually agreed upon time points during the clinical conduct of the study. The second set of samples will be shipped after the bioanalytical laboratory confirms receipt of the first set of samples.
2. Samples will be packaged into cryoboxes and sorted by subject and time point.
3. Prior to shipment, the samples will be appropriately packed in a cooler containing dry ice. Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 72 hours.
4. An electronic manifest will be provided in advance. The shipment will be accompanied by documentation containing the following information: name of the study drug product, protocol number, number of subjects, and number of samples included in the shipment. Expected samples that are not present will be identified.
5. All frozen pharmacokinetic samples will be transferred with accompanying documentation to:

   Alliance Pharma, Inc.
   17 Lee Blvd
   Malvern, PA 19355
   Telephone: 610.296.3152
   Fax: 610.296.3153
   Contact name: Ruth Guan
   Contact e-mail: dzang@alliancepharmaco.com; samples@alliancepharmaco.com

APPENDIX 2 DESCRIPTION AND COMPOSITION OF TEST PRODUCT

Description of the Dosage Form

TBI-223 tablets are supplied as immediate release (IR) or sustained release (SR) or placebo. The description of the tablets and strengths are as follows:

TBI-223 IR tablets 600 mg (IR)

White to off-white, capsule shaped tablets, debossed with "TBA" on one side and "22" on the other

TBI-223 SR Tablets, 600 mg (Prototype 1) (SR1)

White to off-white, capsule shaped tablets, debossed with "TBA" on one side and "11" on the other

Placebo Tablets for TBI-223 IR and SR Tablets 600 mg (Placebo)

White to off-white, capsule shaped tablets, debossed with "TBA" on one side and "17" on the other

Composition of the Drug Product

The composition of the tablets is as follows:

TBI-223 IR tablets, 600 mg

TBI-223, microcrystalline cellulose, hypromellose, crospovidone, colloidal silicon dioxide, magnesium stearate

TBI-223 SR Tablets, 600 mg (Prototype 1) (SR1)

TBI-223, lactose monohydrate, microcrystalline cellulose, hypromellose, colloidal silicon dioxide, magnesium stearate

Placebo Tablets for TBI-223 IR and SR Tablets 600 mg

Microcrystalline cellulose, hypromellose, crospovidone, colloidal silicon dioxide, magnesium stearate.

Container and Closure System

TBI-223 IR Tablets, TBI-223 SR Tablets, and Placebo Tablets are packaged as 30-count in 100 cc round high-density polyethylene (HDPE) bottles and closed with aluminum foil lined heat induction seals and 38 mm polypropylene (PP) child resistant closures (CRC).

APPENDIX 3 DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASE TOXICITY TABLE

Division of Microbiology and Infectious Disease (DMID) Toxicity Table

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

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

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

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of Patients in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.

- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

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

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN

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

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

*Assessment does not apply if a subject is on menses.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment[1]	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required[1]	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea	moderate or persistent; 5-7 loose stools/day or	>7 loose stools/day or bloody diarrhea; or orthostatic	hypotensive shock or physiologic consequences

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	last < 1 week	diarrhea lasting >1 week	hypotension or electrolyte imbalance or >2L IV fluids required	requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

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

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

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

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