Statistical Analysis Plan

A Phase 1, Partially-Blinded, Placebo-Controlled, Randomized Single Ascending Dose (SAD) with a Food Effect Cohort Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TBI-223 in Healthy Adult Participants

Protocol Number: *TBI-223-CL-001*

Protocol Version: *3.0, dated 21-Jan-2020*

SAP Version *2.0*

SAP Issue Date: *28-April-2020*

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Previous SAP Versions

Version 1.0, dated 05-March-2019

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SAP Amendments Before Database Lock

Version	Issue Date	Revision/Addition
2.0	*28-Apr-20*	SAP v2.0 has been updated in line with Protocol v3.0, dated 21-Jan-2020. The following changes affecting the analyses described in SAP v1.0, dated 05-March-2019 are as follows: **Changes to dose cohorts** TBI-223 (1400 mg) suspension was replaced with TBI-223 (2000 mg) suspension. TBI-223 (2600 mg) suspension cohort was added TBI-223 300 mg oral capsule repeat cohort was added. Study Part 2 was added, including, – Arm 1 - TBI-223 SR Tablets 600 mg (Prototype 1). Dose of 1800 mg (3 tablets of 600 mg), under fed conditions – Arm 2 - TBI-223 SR Tablets 600 mg (Prototype 2). Dose of 1800 mg (3 tablets of 600 mg), under fed conditions – Arm 3 - TBI-223 SR Tablets 900 mg (Prototype 3). Dose of 1800 mg (2 tablets of 900 mg), under fed conditions – Arm 4 - TBI-223 IR Tablets 1000 mg. Dose of 2000 mg (2 tablets of 1000 mg), under fasting conditions – TBI-223 IR Tablets 1000 mg. Dose of 2000 mg (2 tablets of 1000 mg), under fed conditions. **Changes to safety analyses** All Enrolled Subjects analysis set was added. Subject Disposition will be summarized for All Enrolled Subjects rather than the Randomized Set.

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Version	Issue Date	Revision/Addition
		Safety data will be tabulated by study part, period (where applicable) and treatment group. SAP sections 4 Sample Size and 5 Randomization were updated to reflect study Parts 1 and 2. **Changes to PK analyses** As of SAP v2.0, PK concentration and parameter data will also be stratified by gender. Description of PK analyses and outputs were updated to reflect protocol and dose group changes.

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1 INTRODUCTION

This document details the planned statistical analyses for the Global Alliance for TB Drug Development, protocol "TBI-223-CL-001" study titled "A Phase 1, Partially-Blinded, Placebo-Controlled, Randomized Single Ascending Dose (SAD) with a Food Effect Cohort Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TBI-223 in Healthy Adult Participants". The proposed analyses are based on the contents of protocol version 3.0, dated 21-Jan-2020 and Protocol Clarification Letter No. 4, dated 24-Feb-2020.

This is a partially blinded, placebo-controlled, randomized, SAD study with a food effect cohort. The study will be conducted at one study center in the United States.

Part 1

Part 1 of the study will have up to 6 planned dose levels. Based on interim pharmacokinetic data obtained during the dose escalation, a dose cohort will be selected to return for additional dosing after a high-calorie, high-fat meal (food-effect cohort).

Part 2

Part 2 of the study will comprise 4 arms each consisting of 6 subjects. Subjects will be assigned to one of the following dosing arms:

Arm 1	TBI-223 SR Tablets (Prototype 1) - 1800 mg dose (3 x 600 mg tablets) under fed conditions
Arm 2	TBI-223 SR Tablets (Prototype 2) - 1800 mg dose (3 x 600 mg tablets) under fed conditions
Arm 3	TBI-223 SR Tablets (Prototype 3) - 1800 mg dose (2 x 900 mg tablets) under fed conditions
Arm 4	TBI-223 IR Tablets - 2000 mg dose (2 x 1000 mg tablets) under fasting conditions

*IR = Immediate Release; SR = Sustained Release

The 6 subjects from Arm 4, who received the IR tablet formulation will be brought back following a 7-day washout period to receive TBI-223 IR Tablets 2000 mg (2 x 1000 mg tablets), under fed conditions. If more than 2 of the 6 subjects drop-out, they will be replaced by heathy volunteers (a minimum of 4 subjects is required to complete the Fed cohort).

Additional cohorts may be enrolled if deemed appropriate (e.g. if bioavailability is lower than expected) by the Sponsor to repeat a dose level, to study other dose levels, change proposed

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cohorts, or to study a different dosage formulation. These 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 have been demonstrated to permit proceeding to the next cohort. The Institutional Review Board (IRB) should be immediately notified of this revised approach for review and approval.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of single doses of TBI-223 oral suspension, TBI-223 oral enteric capsules, and TBI-223 tablet formulations in healthy adult subjects.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To determine the pharmacokinetics of TBI-223 and its metabolite M2 after single doses of TBI-223 oral suspension, TBI-223 oral enteric capsules, and TBI-223 tablet formulations in healthy adult subjects.
- To compare the rate and extent of absorption of a single dose of TBI-223 oral suspension, TBI-223 oral enteric capsules, and TBI-223 tablet formulations when administered in healthy adult subjects either after a high-calorie, high-fat meal or in the fasting state.

3 ENDPOINTS

3.1 Safety Endpoints

Safety assessments will include physical and neurological examinations, vital signs including heart rate and respiratory rate, electrocardiograms (ECGs), cardiac monitoring, adverse events (AEs), and clinical laboratory tests (including hematology, serum chemistry, coagulation, and urinalysis).

3.2 Pharmacokinetic Endpoints

Serial blood samples will be collected pre-dose and post-dose through 72 hours to determine concentrations of TBI-223 and its metabolite (M2) in plasma.

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Noncompartmental pharmacokinetic parameters of AUC_{last}, AUC_{inf}, C_{max}, T_{max}, C_{last}, T_{last}, $AUC_{Extrap\%}$, λz, and $T_{½}$ will be calculated from plasma concentrations of TBI-223 (parent) and TBI-223 M2 (metabolite); CL/F and V_z/F will be calculated for TBI-223 only.

For Part 1, pharmacokinetic parameters will be summarized by cohort using descriptive statistics. Dose proportionality will be assessed using the power model approach (Cohorts 1-7, under fasted conditions). The 90% confidence intervals for geometric mean ratios, fed-to-fasted, of AUC_{last}, AUC_{inf}, and C_{max} will be determined as appropriate for Cohort 5.

For Part 2, pharmacokinetic parameters will be summarized by cohort and treatment/arm using descriptive statistics. The 90% confidence intervals for geometric mean ratios, test-to-reference, of AUC_{last}, AUC_{inf}, and C_{max} will be determined as appropriate for Cohorts 8 and 9.

Additional pharmacokinetic parameters may be calculated if deemed appropriate.

4 SAMPLE SIZE

For Part 1, up to 50 subjects are planned to be enrolled in the study.

Fasting Cohorts: It was planned to enroll up to 48 subjects in a total of 6 cohorts of 8 subjects each (6 to receive active drug and 2 to receive placebo).

Food-effect Cohort: One of the 6 planned dose cohorts will be selected to enroll 10 subjects (8 active and 2 placebo) who will receive TBI-223 or placebo under both fasting and fed conditions.

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

For Part 2, 24 subjects will be enrolled. The 6 subjects who received the IR tablet formulation under fasted conditions will return after a 7-day washout and receive the IR tablet formulation under fed conditions. If more than 2 subjects of these 6 subjects drop-out, they will be replaced by heathy volunteers (a minimum of 4 subjects are needed to complete the cohort).

The number of subjects selected for the study was based on the adequate number considered to provide sufficient safety data. This study has not been formally powered.

5 RANDOMIZATION

Each subject in Part 1 will receive an assigned treatment (active or placebo) based on the randomization schedule prepared by the unblinded statistician. The first cohort will be separated into two groups. A sentinel group of 3 subjects (2 active and 1 placebo) will be dosed at least 24

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hours before the remaining 5 subjects (4 active and 1 placebo). The remaining cohorts will be dosed in 2 groups of 4 subjects each (3 active and 1 placebo), 24 hours apart. Based on exposure levels, subjects in one of the dose levels will return after a 7-day minimum washout or 5 half-lives of the drug (whichever is longer) to receive the same dose under fed conditions. All subjects and clinical staff (except for the unblinded pharmacy staff) will be blinded to treatment.

Subjects in Part 1 who participate in the repeat cohort will receive a different treatment formulation. In Part 2, subjects will be non-randomized and unblinded.

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be definitive and the final clinical study report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Sets

Subjects excluded from the analysis sets and the reason for their exclusion will be listed in Appendix 16.2.

6.1.1 All Enrolled Subjects

Enrolled subjects include all subjects who have given informed consent to participate in the study.

6.1.2 Randomized Set

The Randomized Set includes all subjects to whom a treatment was randomly assigned.

6.1.3 Safety Analysis Set

The Safety Analysis Set includes all subjects who received any dose of study drug.

6.1.4 PK Analysis Set

The PK Analysis Set includes all subjects with sufficient data to derive PK parameters.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

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6.2.1 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

6.2.2 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the single dose of study drug in the relevant study part and dosing period.

6.2.3 Early Withdrawal Assessments

Early withdrawal assessments will be tabulated with End of Study (EOS).

6.2.4 Duration/Study Day

Study day will be calculated as the number of days from single dose of study drug in the relevant dosing period (fasted or fed).

- date of the event – date of the first dose of study drug + 1, for events on or after first dose
- date of the event – date of the first dose of study drug, for events before first dose.

6.2.5 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates, however in the rare case that an AE start date or time is missing, and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken and it will be assumed that the AE occurred after first dosing.

All dates presented in the individual subject listings will be as recorded on the eCRF.

6.2.6 Inexact Values

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.7 Electrocardiogram Data

For ECG data recorded on continuous scales, if more than one value is recorded at a time point, the mean value rounded to the integer will be presented. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

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6.2.8 Unscheduled Visits

Only scheduled post-baseline assessments will be tabulated. Post-baseline repeat/unscheduled assessments will not be summarized but will be listed in the relevant appendices to the CSR.

6.2.9 PK Parameters

Blood Samples for PK analysis in plasma will be collected at pre-dose (0), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 30, 36, 42, 48, and 72 hours post-dose.

Concentration-time data for TBI-223 (parent) and TBI-223 M2 (metabolite) will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.1, Certara, L.P)[1].

During the pharmacokinetic analysis, concentrations below the limit of quantitation (BLQ) up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as "missing".

The following PK parameters will be calculated for TBI-223 and TBI-223 M2 for Parts 1 and 2:

Parameter	Definition
C_{max}	Maximum plasma concentration, determined directly from individual concentration-time- data
T_{max}	Time of the maximum plasma concentrations
C_{last}	Last quantifiable plasma concentration determined directly from individual concentration-time data
T_{last}	Time of the last quantifiable plasma concentration
AUC_{last}	Area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration (C_{last}), as calculated by the linear trapezoidal rule
AUC_{inf}	Area under the plasma concentration-time- curve from the time of dosing extrapolated to infinity, calculated as:

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Parameter	Definition
	$AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$, where λ_z is the apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve
AUC_{Extrap}	The percentage of AUC_{inf} based on extrapolation, calculated as: $[1 - (AUC_{last}/AUC_{inf})]* 100$
λ_z (K_{el} , Lambda z)	The apparent elimination rate constant λ_z will be calculated as the negative of the slope of the linear regression through the terminal log-linear segment of the plasma concentration-time curve; the range of data to be used will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time.
$T_{½}$	The observed terminal elimination half-life, calculated as: $T_{½} = \ln(2)/\lambda_z$
CL/F	The apparent total plasma clearance after an oral dose, calculated as: CL/F=Dose/AUC_{inf}, where F is the bioavailability, (calculated for parent only)
V_z/F	The apparent volume of distribution after an oral dose, calculated as: V_z/F=Dose/(AUC_{inf} x λ_z), where F is the bioavailability, (calculated for parent only)
DN_C_{max}	For Cohort 8: maximum plasma concentration for TB-223 SR prototype tablets, 1800 mg, dose-normalized to 2000 mg
DN_AUC_{last}	For Cohort 8, area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration (C_{last}), as calculated by the linear trapezoidal rule, for TB-223 SR prototype tablets, 1800 mg, dose-normalized to 2000 mg

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Parameter	Definition
DN_AUC$_{inf}$	For Cohort 8, area under the plasma concentration-time- curve from the time of dosing extrapolated to infinity, calculated as: AUC$_{inf}$ = AUC$_{last}$ + C$_{last}$/λ_z, where λ_z is the apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve, for TB-223 SR prototype tablets, 1800 mg, dose-normalized to 2000 mg

Lambda-z (λ_z) Acceptance Criteria

The following criteria will be used to report lambda-z and related parameters:

- At least 3 quantifiable concentration-time points should be used in the regression
- C_{max} or data prior to C_{max} should not be included in the regression
- Adjusted R^2 should be ≥ 0.8000

If these acceptance criteria are not met, lambda-z and descriptive parameters such as the time range for the regression, adjusted R^2, etc. will be retained in a parameter listing for informational purposes. Lambda-z will be excluded from summary statistics and from subsequent PK calculations; parameters calculated using lambda-z (e.g. $t_{1/2}$, AUC$_{inf}$, CL/F, and V_z/F) will be reported as ND (not determinable).

If lambda-z acceptance criteria are met and AUC$_{inf}$ is estimable, the following criteria are used to report AUC$_{inf}$:

- The percentage of AUC$_{inf}$ based on extrapolation should be <30.0%.

If the percentage of AUC$_{inf}$ based on extrapolation is 30.0% or greater, AUC$_{inf}$ and AUC$_{Extrap}$ will be retained in a PK parameter listing for informational purposes; these parameters will be excluded from summary statistics, subsequent PK calculations (e.g. CL/F, V_z/F), and statistical analysis (e.g. ANOVA).

6.3 Conventions

All clinical data listings, summaries and statistical analyses will be generated using SAS (Version 9.4 or higher)[2]. Summaries of clinical data will be presented by treatment period and treatment group or overall.

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PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 8.1) or SAS (Version 9.4 or higher). PK concentration data will be summarized by study part, analyte, and treatment at each nominal sample time. PK parameter data will be summarized by study part, analyte, and treatment. PK concentration and parameter data will also be stratified by gender.

Treatment group labels will be displayed as follows:

Part 1 / Oral Suspension / Period 1 (Fasted)

Placebo	TBI-223 50 mg	TBI-223 100 mg	TBI-223 300 mg	TBI-223 600 mg	TBI-223 1200 mg	TBI-223 2000 mg	TBI-223 2600 mg

Part 1 / Oral Suspension / Period 2 (Fed)

Placebo	TBI-223 1200 mg

Part 1 / Capsule Formulation / Repeat Cohort

TBI-223 300 mg Capsule

Part 2 / Tablet Formulation / Period 1

TBI-223 1800 mg SR-1 tablet (Fed)	TBI-223 1800 mg SR-2 tablet (Fed)	TBI-223 1800 mg SR-3 tablet (Fed)	TBI-223 2000 mg IR tablet (Fasted)

Part 2 / Tablet Formulation / Period 2

TBI-223 2000 mg IR tablet (Fed)

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Adverse Event summaries will be displayed as follows:

Part 1 / Oral Suspension and Capsule Formulation

Placebo	TBI-223 50 mg	TBI-223 100 mg	TBI-223 300 mg	TBI-223 300 mg Capsule	TBI-223 600 mg	TBI-223 1200 mg (Fasted)	TBI-223 1200 mg (Fed)	TBI-223 2000 mg	TBI-223 2600 mg	Overall

The Placebo column will include Period 1 (Fasted) and Period 2 (Fed) events.

Placebo is not administered to subjects in the repeat cohort who will receive capsule formulation.

Overall column will include all reported events during Part 1.

Part 2 / Tablet Formulation

TBI-223 1800 mg SR-1 tablet (Fed)	TBI-223 1800 mg SR-2 tablet (Fed)	TBI-223 1800 mg SR-3 tablet (Fed)	TBI-223 2000 mg IR tablet (Fasted)	TBI-223 2000 mg IR tablet (Fed)	Overall

Overall column will include all reported events during Part 2.

Listings will be sorted in the following order: Study part, period (where applicable), treatment group (Placebo followed by TBI-223 in ascending dose order), subject number, parameter, and visit unless otherwise stated. All data will be listed.

For clinical data, continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

PK data (concentration-time data and PK parameters) will be summarized by the number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%), calculated as (SD/Mean)*100. In addition, the geometric mean and geometric CV%, calculated as SQRT[exp(SD^2 of log transformed data)-1]*100, will be reported for C_{max} and AUCs.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless

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otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

6.3.1 Decimal Places

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

For PK data, individual concentrations will be reported to 3 significant figures and individual PK parameters will be reported to the precision as stated in Section 6.2.9. For summary statistics, n will be reported as a whole number; mean, standard deviation, median, minimum, maximum, and geometric mean will be reported to the same precision as for individual data. CV% and geometric CV% will be reported to 2 decimal places; p-values will be reported to 4 decimal places. Percent ratios of the geometric least squares means and associated 90% confidence intervals will be reported to 2 decimal places.

6.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects in each analysis set will be summarized by study part, period (where applicable), treatment group and overall for all enrolled subjects.
- The number of early withdrawals and the reasons for withdrawals will be tabulated by study part, period (where applicable), treatment group and overall for all enrolled subjects.

6.5 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2.

6.6 Baseline Comparability

The comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed. The Safety Analysis Set will be used to summarize all baseline and demographic data.

6.7 Demographic Data

Standard continuous or categorical variable summaries will be presented by treatment group for the following variables based on the Safety Analysis Set.

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- Age at Informed Consent (years)
- Sex
- Ethnicity
- Race, where more than one race is selected the subject will be presented under the 'Multiple races' category in the summary but each selected race will be identified in the listing.
- Weight at Screening (kg)
- Height at Screening (cm)
- BMI at Screening (kg/m^2)

6.8 Medical History

Separate listings of previous and ongoing conditions at Screening will be presented for the Safety Set. Conditions will be coded using the Medical Dictionary of Regulated Activities (MedDRA version 21.0 or higher) primary system organ class (SOC) and preferred term (PT). Any medical condition will be classed as resolved if a stop date is recorded, otherwise, the condition will be classed as ongoing.

6.9 Prior and Concomitant Medications

Prior and concomitant medications will be listed for the Safety Analysis Set. Prior medications are defined as all medications starting and stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug. Each concomitant medication will be assigned to the last study drug taken prior to starting the concomitant medication. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary B3 – September 2018 version.

6.10 Exposure to Study Drug

All dosing information will be listed.

6.11 Pharmacokinetic Analyses

Concentration-time data will be tabulated by nominal time, analyte, and cohort using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero.

Mean and individual subject concentration-time data will be presented graphically on linear and semi-logarithmic scales. Mean concentration-time data will be presented for all doses and for fed vs. fasted cohorts. Mean data will be plotted using nominal sample times, and individual data will

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be plotted using actual times. For all subject plots (spaghetti plots, all subjects per treatment in one plot), subjects will be identified by subject number in the legend.

PK parameters will be calculated as described in Section 6.2.9.

PK parameters will be summarized by analyte and cohort using descriptive statistics.

Part 1; Dose Proportionality (Cohorts 1-7, fasted conditions):

The pharmacokinetic parameters C_{max}, AUC_{last}, and AUC_{inf} for TBI-223 for fasted cohorts will be compared across doses to assess dose proportionality (i.e., proportionality of a change in systemic exposure with a change in dose). Statistical analyses will be done using a power model (Smith, 2000) of the following general form,

$$\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon,$$

where

PK is the pharmacokinetic parameter tested (e.g. C_{max} or AUC)

$\ln(\beta_0)$ is the y-intercept,

β_1 is the slope (a value of $\beta_1 \approx 1$ indicates linearity), and

ε is an error term

The estimate of β_1 with the 90% CIs will be reported along with the dose range for proportionality.

Part 1; Food Effect (Cohort 5):

Statistical comparison of the PK parameters of exposure (C_{max}, AUC_{last}, and AUC_{inf}) will be performed using an Analysis of Variance (ANOVA) model for a 2-way crossover design on the ln-transformed data with treatment as the fixed effects and subject as a random effect. Conclusions regarding the results of the statistical analysis of PK parameters across treatments will be based on the ratio of the geometric means expressed as a percent (100×Fed/Fasted) and the 90% confidence interval about the ratio. A lack of food effect will be demonstrated if the 90% confidence intervals are fully contained within the limits of 80.00% to 125.00%.

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Part 1; Cohort 3 Repeat:

Statistical comparison of the PK parameters of exposure (C_{max}, AUC_{last}, and AUC_{inf}) will be performed using an Analysis of Variance (ANOVA) model for a two-way crossover design on the ln-transformed data with treatment as a fixed effect and subject as a random effect. Conclusions regarding the results of the statistical analysis of PK parameters across treatments will be based on the ratio of the geometric means expressed as a percent (100×Test/Reference; TBI-223 oral enteric capsules, Cohort 3 repeat vs. TBI-223 oral suspension, Cohort 3) and the 90% confidence interval about the ratio. Similar bioavailability will be demonstrated if the 90% confidence intervals are fully contained within the limits of 80.00% to 125.00%.

Part 2; Cohorts 8 and 9:

Statistical comparison of the PK parameters of exposure (C_{max}, AUC_{last}, and AUC_{inf}) will be performed using an Analysis of Variance (ANOVA) model for a parallel design on the ln-transformed data with treatment as a fixed effect. Conclusions regarding the results of the statistical analysis of PK parameters across treatments will be based on the ratio of the geometric means expressed as a percent (100×Test/Reference) and the 90% confidence interval about the ratio. The following comparisons will be made:

- IR, 2000 mg (2 x 1000 mg tablets) / FED (Cohort 9) vs. IR, 2000 mg (2 x 1000 mg tablets) / FASTED (Cohort 8)
- SR (Prototype 1, 2 or 3), 1800 mg (2 x 900 mg tablets) / FED (Cohort 8) vs. , 2000 mg (2 x 1000 mg tablets) / FASTED (Cohort 8)
- SR (Prototype 1, 2 or 3), 1800 mg (2 x 900 mg tablets) / FED (Cohort 8) vs. IR, 2000 mg (2 x 1000 mg tablets) / FED

Note: 1800 mg TBI-223 SR Tablets will be dose-normalized to 2000 mg for the purpose of statistical comparisons.

6.12 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Analysis Set.

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6.12.1 Adverse Events

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug through the end-of-study follow-up call (Day 11).
- Any pre-existing AE that has worsened in severity on or after the first dose through the end-of-study follow-up call (Day 11).

Relatedness of an AE to treatment is defined as Not Related, Unlikely, Possible, Probable or Certain. A treatment-related AE is defined as any AE classified as possibly, probably or certainly related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Severity of AEs will be graded using the Division of Microbiology and Infectious Disease (DMID) Toxicity Grade November 2007 version: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially Life-Threatening). Maximum grade will be assumed for an AE with missing grade.

The following tables will be presented for AEs:

- Overall incidence and number of AEs, SAEs, TEAEs leading to withdrawal.
- TEAEs by system organ class and preferred term, incidence and number of events
- Treatment-related TEAEs by system organ class and preferred term, incidence and number of events
- TEAEs by system organ class, preferred term and maximum grade, incidence
- TEAEs by system organ class, preferred term and relationship, incidence
- Listing of TEAEs Leading to Early Withdrawal (presented in the Table section of the appendices)
- Listing of Serious TEAEs (presented in the Table section of the appendices)
- Listing of Deaths (presented in the Table section of the appendices)

System organ class will be presented in descending order of overall frequency and then alphabetically. Preferred terms will be displayed in descending order of overall frequency and then alphabetically.

Where a subject reports more than one AE per system organ class and preferred term they will only be counted once for the most severe event or the most related event.

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All AEs will be listed.

6.12.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by study part, period (where applicable), treatment group and visit for each hematology, serum chemistry, coagulation and urinalysis parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

A listing of any clinically significant laboratory measurements recorded throughout the study will be presented.

6.12.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by study part, period (where applicable) and treatment group at each visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath/min)
- Body temperature (degrees Celsius)
- Pulse oximetry (%)

All vital sign data will be listed.

6.12.4 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated by study part, period (where applicable) and treatment group at each post-baseline assessment:

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS complex (ms)
- QT interval (ms)

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- QTc interval (ms)
- QTc interval (ms) [Bazett's formula - QTcB]
- QTc interval (ms) [Fridericia's formula - QTcF]

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS) from baseline to each post-baseline assessment will be presented. All ECG data, including details of any abnormalities, will be listed.

6.12.5 Cardiac Telemetry (Holter) Data

Data relating to the collection of cardiac telemetry (Holter) data will be listed. Timings of 12-lead ECGs extracted from the continuous Holter recording will be collected on the eCRF but will not be listed for this study.

6.12.6 Physical Examination

Shift tables for the observed status of each of the body systems (Normal, Abnormal NCS, and Abnormal CS) will be tabulated by study part, period (where applicable) and treatment group at each post-baseline assessment. All data, including details of clinically significant findings will be listed.

6.12.7 Neurological Examination

Shift tables for the observed status of each neurological aspect (Normal, Abnormal NCS, and Abnormal CS) will be tabulated by study part, period (where applicable) and treatment group at each post-baseline assessment. All data, including details of clinically significant findings will be listed.

7 CHANGES TO PLANNED PROTOCOL ANALYSIS

No changes to the planned analyses have been identified.

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8 REFERENCES

1. Phoenix™ WinNonlin® (Version 8.1, Certara L.P)
2. SAS Institute Inc., Cary, NC, 27513, USA

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9 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Please note, PK Table, Figure and Listing numbers and titles are subject to change and may be consolidated upon final analysis.

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1	Subject Disposition, Early Withdrawals - All Enrolled Subjects	IP	
14.1.2	**Demographics**		
14.1.2.1	Demographics - Safety Analysis Set	IP	
14.1.3	**Baseline Characteristics**		
	Not Applicable		
14.2	**Efficacy Data**		
	Not Applicable		
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1	Adverse Events, Overall Summary of Treatment-Emergent Adverse Events (TEAEs) – Safety Analysis Set	IP	
14.3.1.2	Adverse Events, TEAEs by Primary System Organ Class and Preferred Term – Safety Analysis Set	IP	
14.3.1.3	Adverse Events, Treatment-Related TEAEs by Primary System Organ Class and Preferred Term – Safety Analysis Set	IP	
14.3.1.4	Adverse Events, TEAEs by Primary System Organ Class, Preferred Term and Maximum Grade – Safety Analysis Set	IP	

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Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.5	Adverse Events, TEAEs by Primary System Organ Class, Preferred Term and Nearest Relationship – Safety Analysis Set	IP	
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1	TEAEs Leading to Early Withdrawal, Listing – Safety Analysis Set	IP	
14.3.2.2	Serious TEAEs, Listing – Safety Analysis Set	IP	
14.3.2.3	Deaths, Listing – Safety Analysis Set	IP	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1	Listing of Clinically Significant Laboratory Values – Safety Analysis Set	IP	
14.3.5	**Extent of Exposure, Dosage Information, and Compliance**		
	Not Applicable		
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1	Vital Signs, Descriptive Statistics – Safety Analysis Set	IP	
14.3.6.2	Physical Examination, Change from Baseline – Safety Analysis Set	IP	
14.3.6.3	Neurological Examination, Change from Baseline – Safety Analysis Set	IP	
14.3.7	**Other Safety**		
14.3.7.1	Hematology Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.2	Hematology Data, Normal Range Shifts – Safety Analysis Set	IP	
14.3.7.3	Serum Chemistry Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.4	Serum Chemistry Data, Normal Range Shifts – Safety Analysis Set	IP	
14.3.7.5	Coagulation Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.6	Coagulation Data, Normal Range Shifts – Safety Analysis Set	IP	
14.3.7.7	Urinalysis Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.8	Urinalysis Data, Normal Range Shifts – Safety Analysis Set	IP	
14.3.7.9	12-Lead ECG Data, Descriptive Statistics – Safety Analysis Set	IP	

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Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.7.10	12-Lead ECG Data, Overall Interpretation – Safety Analysis Set	IP	
14.3.8	**Concomitant Medication**		
	Not Applicable		
14.4	**PK Tables**		
14.4.1	Descriptive Statistics for Concentration-Time Data of TBI-223 and TBI-223 M2 after Single Doses of TBI-223 (Part 1; Cohorts 1-7)	MR	
14.4.2	Descriptive Statistics for Concentration-Time Data of TBI-223 and TBI-223 M2 after Single Doses of TBI-223 Oral Suspension (Part 1; Cohorts 1-7) by Gender		
14.4.3	Descriptive Statistics for Concentration-Time Data of TBI-223 and TBI-223 M2 after Single Doses of TBI-223 (Part 2; Cohorts 8 and 9)	MR	
14.4.4	Descriptive Statistics for Concentration-Time Data of TBI-223 and TBI-223 M2 after Single Doses of TBI-223 (Part 2; Cohorts 8 and 9) by Gender	MR	
14.4.5	Plasma Pharmacokinetic Parameters of TBI-223 after Single Doses of TBI-223 (Part 1; Cohorts 1-7)	MR	
14.4.6	Plasma Pharmacokinetic Parameters of TBI-223 after Single Doses of TBI-223 (Part 1; Cohorts 1-7) by Gender		
14.4.7	Plasma Pharmacokinetic Parameters of TBI-223 M2 after Single Doses of TBI-223 (Part 1; Cohorts 1-7)		
14.4.8	Plasma Pharmacokinetic Parameters of TBI-223 M2 after Single Doses of TBI-223 (Part 1; Cohorts 1-7) by Gender		
14.4.9	Plasma Pharmacokinetic Parameters of TBI-223 after Single Doses of TBI-223 (Part 2; Cohorts 8 and 9)		
14.4.10	Plasma Pharmacokinetic Parameters of TBI-223 after Single Doses of TBI-223 (Part 2; Cohorts 8 and 9) by Gender		
14.4.11	Plasma Pharmacokinetic Parameters of TBI-223 M2 after Single Doses of TBI-223 (Part 2; Cohorts 8 and 9)		
14.4.12	Plasma Pharmacokinetic Parameters of TBI-223 M2 after Single Doses of TBI-223 (Part 2; Cohorts 8 and 9) by Gender		

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Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.4.13	Assessment of Dose Proportionality Following Single-Dose Administrations of TBI-223 under Fasted Conditions (Part 1; Cohorts 1-7)	MR	
14.4.14	Statistical Analysis of the Natural Log-Transformed- Systemic Exposure of TBI-223 after a Single 1200 mg Dose of TBI-223 Oral Suspension under Fed (Test) and Fasted (Reference) Conditions (Part 1; Cohort 5)	MR	
14.4.15	Statistical Analysis of the Natural Log-Transformed- Systemic Exposure of TBI-223 after a Single 300 mg Dose of TBI-223 Capsule Formulation (Cohort 3 Repeat; Part 1) and a Single 300 mg Dose of TBI-223 Oral Suspension (Cohort 3; Part 1)		
14.4.16	Statistical Analysis of the Natural Log-Transformed- Systemic Exposure of IR, 2000 mg (2 x 1000 mg TBI-223 tablets) under Fed Conditions (Cohort 9) and IR, 2000 mg (2 x 1000 mg TBI-223 tablets) under Fasted Conditions (Cohort 8)	MR	
14.4.17	Statistical Analysis of the Natural Log-Transformed- Systemic Exposure of SR (Prototypes 1, 2, and 3), 1800 mg (2 x 900 mg TBI-223 tablets) under Fed Conditions (Cohort 8) and IR, 2000 mg (2 x 1000 mg TBI-223 tablets) under Fasted Conditions (Cohort 8)	MR	
14.4.18	Statistical Analysis of the Natural Log-Transformed- Systemic Exposure of SR (Prototypes 1, 2, and 3), 1800 mg (2 x 900 mg TBI-223 tablets) under Fed Conditions (Cohort 8) and IR, 2000 mg (2 x 1000 mg TBI-223 tablets) under Fed Conditions (Cohort 9)	MR	

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Figure Number	Figure Title		
14.4.1	Mean Plasma Concentration-Time Profiles of TBI-223 and TBI-223 M2 after Single Doses of TBI-223 Administered under Fasted Conditions (Part 1; Cohorts 1-7) on Linear and Semi Logarithmic Scales	MR	
14.4.2	Mean Plasma Concentration-Time Profiles of TBI-223 and TBI-223 M2 after a Single 1200 mg Dose of TBI-223 Oral Suspension under Fed and Fasted Conditions (Part 1; Cohort 5) on Linear and Semi Logarithmic Scales	MR	
14.4.3	Mean Plasma Concentration-Time Profiles of TBI-223 and TBI-233 M2 after a Single 300 mg Dose of TBI-223 Oral Suspension (Cohort 3; Part 1) and a Single 300 mg Dose of TBI-223 Capsule Formulation (Cohort 3 Repeat; Part 1) on Linear and Semi Logarithmic Scales	MR	
14.4.4	Mean Plasma Concentration-Time Profiles of TBI-223 and TBI-223 M2 after Single Doses of TBI-223 (Cohorts 8, and 9; Part 2) on Linear and Semi Logarithmic Scales	MR	
14.4.5	Mean Plasma Concentration-Time Profiles of TBI-223 and TBI-223 M2 for Males and Females by Cohort (Part 1) on Linear and Semi Logarithmic Scales		
14.4.6	Mean Plasma Concentration-Time Profiles of TBI-223 and TBI-223 M2 for Males and Females by Cohort (Part 2) on Linear and Semi Logarithmic Scales		
14.4.7	All Subject Plasma Concentration-Time Profiles of TBI-223 and TBI-223 M2 after Single Doses of TBI-223 (Cohorts 1-7; Part 1) on Linear and Semi Logarithmic Scales	MR	
14.4.8	All Subject Plasma Concentration-Time Profiles of TBI-223 and TBI-223 M2 after Single Doses of TBI-223 (Cohorts 8 and 9; Part 2) on Linear and Semi Logarithmic Scales	MR	
14.4.9	Individual Plasma Concentration-Time Profiles of TBI-223 and TBI-223 M1 after a Single 1200 mg Dose of TBI-223 Oral Suspension under Fed and Fasted Conditions (Part 1, Cohort 5) on Linear and Semi Logarithmic Scales	MR	
14.4.10	Individual Plasma Concentration-Time Profiles of TBI-223 and TBI-223 M2 after a Single Dose of TBI-223 Oral Suspension (Cohort 3; Part 1) and a Single Dose of	MR	

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Figure Number	Figure Title		
	TBI-223 Capsule Formulation (Cohort 3 Repeat; Part 1) on Linear and Semi Logarithmic Scales		
14.4.11	Concentration-Time Profiles for TBI-223 and TBI-223 M2 with Linear Regression for Estimating the Terminal Elimination Rate	MR	

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Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition - All Enrolled Subjects	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations – Safety Analysis Set	IP	
16.2.3	**Subjects Excluded from The Efficacy Analyses**		
16.2.3.1	Analysis Sets - All Enrolled Subjects	IP	
16.2.4	**Demographic Data**		
16.2.4.1	Demographic Data – Safety Analysis Set	IP	
16.2.4.2	Previous and Ongoing Medical History – Safety Analysis Set	IP	
16.2.5	**Compliance and/or Drug Concentration Data**		
16.2.5.1	PK Sampling Data – Safety Analysis Set	IP	
16.2.5.2	Dosing Information – Safety Analysis Set	IP	
16.2.5.3	Prior and Concomitant Medication – Safety Analysis Set	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Plasma TBI-223 and TBI-223 M2 Concentration Listing by Subject (Part 1)	MR	
16.2.6.2	Plasma TBI-223 and TBI-223 M2 Concentration Listing by Subject (Part 2)		
16.2.6.3	Terminal Elimination Rate of TBI-223 and TBI-223 M2 in Plasma for Individual Subjects (Part 1)	MR	
16.2.6.4	Terminal Elimination Rate of TBI-223 and TBI-223 M2 in Plasma for Individual Subjects (Part 2)		
16.2.6.5	PK Output for TBI-223 and TBI-223 M2	MR	
16.2.6.6	Statistical Analysis SAS Output for Dose Proportionality (Part 1)	MR	
16.2.6.7	Statistical Analysis SAS Output for Food Effect Assessment (Part 1, Cohort 5)	MR	
16.2.6.8	Statistical Analysis SAS Output for Formulation Effect Assessment (Part 1, Cohort 3 and Cohort 3 Repeat)	MR	
16.2.6.9	Statistical Analysis SAS Output for Food Effect Assessment (IR tablets; Part 2)	MR	
16.2.6.10	Statistical Analysis SAS Output (SR Fed vs. IR Fasted; Part 2)	MR	

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Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.6.11	Statistical Analysis SAS Output (SR Fed vs IR Fed; Part 2)	MR	
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Event Data – Safety Analysis Set	IP	
16.2.8	**Individual Laboratory Measurement and Other Safety**		
16.2.8.1	Hematology Data – Safety Analysis Set	IP	
16.2.8.2	Serum Chemistry Data – Safety Analysis Set	IP	
16.2.8.3	Coagulation Data – Safety Analysis Set	IP	
16.2.8.4	Urinalysis Data – Safety Analysis Set	IP	
16.2.8.5	Drug and Alcohol Screening Data – Safety Analysis Set	IP	
16.2.8.6	Serology Data – Safety Analysis Set	IP	
16.2.8.7	Pregnancy Test Data – Safety Analysis Set	IP	
16.2.8.8	Vital Signs Data – Safety Analysis Set	IP	
16.2.8.9	Physical Examination Data – Safety Analysis Set	IP	
16.2.8.10	Neurological Examination Data – Safety Analysis Set	IP	
16.2.8.11	12-Lead ECG Data – Safety Analysis Set	IP	
16.2.8.12	Cardiac Telemetry (Holter) Collection Data – Safety Analysis Set	IP	
16.2.8.13	Breath Strip Application Data – Safety Analysis Set	IP	

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