STATISTICAL ANALYSIS PLAN: INDV-2000-101

Protocol Title: A Phase I, Double-blind, Placebo-controlled, Randomized, Single Ascending Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of INDV-2000 (C4X_3256) under Fasting and Fed Conditions in Healthy Volunteers

Final Version: 30 March 2021

NCT: NCT04413552

[redacted]

STATISTICAL ANALYSIS PLAN

For:

Indivior Inc.

PROTOCOL No. *INDV-2000-101*

A Phase I, Double-blind, Placebo-controlled, Randomized, Single Ascending Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of INDV-2000 (C4X_3256) under Fasting and Fed Conditions in Healthy Volunteers

[redacted]

Version: Final 1.0

Date: 2021/03/30

[redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

We have carefully read this statistical analysis plan and agree it contains the necessary information required to handle the statistical analysis of study data.

[redacted]

On behalf of the Sponsor:

[redacted]

[redacted]

VERSION CONTROL

Version	Date	Author	Description of Changes
1.0	2021/03/30	[redacted]	

[redacted]

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[redacted]

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ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma drug concentration versus time curve
BMI	Body mass index
CRF	Case report form
CS	Clinically significant
CSR	Clinical study report
CV%	Coefficient of variation
DBP	Diastolic blood pressure
DTS	Deviation tracking system
DMP	Data Management Plan
DRSC	Data Review and Safety Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
FDA	Food and Drug Administration
IMP	Investigational Medicinal Product
Ln	Natural log
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCA	Non compartmental Analysis
NCS	Not clinically significant
NOAEL	No Observed Adverse Effect Level
OX1R	Orexin-1 receptor
PK	Pharmacokinetic(s)
PT	Preferred term
QTcF	QT interval corrected with Fridericia's formula
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error

[redacted]

SOC	System organ class
SOP	Standard operating procedure
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures, and listings
UDS	Urine Drug Screen
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White blood cell
WHODrug	World Health Organization Drug

[redacted]

1 INTRODUCTION

This study is a phase I, Double-blind, Placebo-controlled, Randomized, Single Ascending Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of INDV-2000 (C4X_3256) under Fasting and Fed Conditions in Healthy Volunteers.

[redacted]. Target population will be healthy male and non-childbearing potential female subjects aged 18 to 55 years, body mass index (BMI) 18.0 to 32.0 kg/m^2.

The study will be conducted in 2 parts:

Part I: Double-blind, placebo-controlled, randomized, single ascending dose (SAD) study with INDV-2000 in fasted condition.

Part II: Open, cross-over, food interaction, single-dose study with INDV-2000, which will be given once under fasting conditions and once at completion of a standard Food and Drug Administration (FDA) high-fat breakfast.

This statistical analysis plan (SAP) provides a detailed description of the presentation of data collected during the study as well as the statistical methods and procedures to be implemented for the analyses of pharmacokinetic (PK) data from protocol INDV-2000-101.

The analyses described in the SAP are based upon the final amendment 02 protocol version 3.0, dated 10 December 2020.

[redacted]

2 STUDY OBJECTIVES

The objectives of the study and corresponding study endpoints are detailed in Table 1.

Table 1: Objectives and related endpoints

Objective	Endpoint(s)	Analysis
Primary		
Determine the safety and tolerability of INDV-2000 over a proposed range of doses from 1 mg [redacted]	Incidence, seriousness, severity, and relationship to Investigational Medicinal Product (IMP) of treatment-emergent adverse events (TEAEs) in the Safety population	Refer to Section 9.1.9
Secondary		
Determine the maximum tolerated single dose of INDV-2000	Clinical safety assessments: Changes from baseline in laboratory evaluations, electrocardiogram (ECG) parameters, vital signs, physical examination	Refer to Sections 9.1.12, 9.1.13, 9.1.14, 9.1.15
Characterize pharmacokinetics for single doses of INDV-2000	Part I: Single Ascending Dose (SAD) under fasted condition: Plasma INDV-2000 and M12 C_{max}, t_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{(t1\text{-}t2;\ \text{where t1-t2 represents urine collection interval t1-t2})}$, $t_{1/2;}$ plasma INDV-2000 CL/F and V_z/F. Additional PK parameters will be estimated to support these PK endpoints	Refer to Section 7
Determine potential effects of a high-fat meal on drug absorption and exposure	Part II: Food interaction: Plasma INDV-2000 and M12 C_{max}, t_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{1/2}$; plasma INDV-2000 CL/F and V_z/F.	Refer to Section 7
[redacted]		

[redacted]

3 STUDY DESIGN

3.1 General Description

This study will be conducted in 2 parts:

Part I: Double-blind, placebo-controlled, randomized, single ascending dose (SAD) study with INDV-2000 in fasted condition.

Healthy subjects who meet all eligibility criteria and provide informed consent will be randomized in cohorts of 8 subjects, with 6 subjects receiving active drug and 2 subjects receiving placebo. The proposed doses will be: 1 mg, 5 mg, 20 mg, 50 mg and 120 mg, [redacted]

The goal for Part I is to identify the maximum well-tolerated (MTD) single dose. A sentinel group of 2 subjects will be randomized to active or placebo (1 active; 1 placebo) and will be dosed ahead of the rest of each cohort. A review of sentinel group safety data for 24 hours after dosing will be completed before IMP administration will continue in the remaining 6 subjects (5 active; 1 placebo) of each cohort.

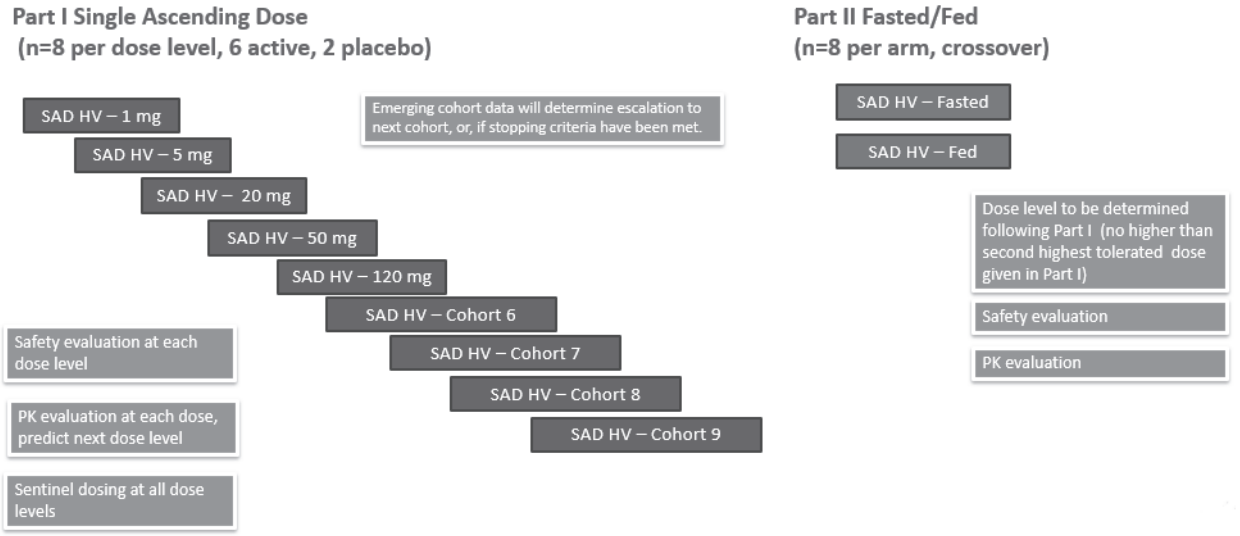
Dose escalation decisions between cohorts will be based on a review of available safety data up to 72 hours post-dose, particularly TEAEs, vital signs, ECGs, clinical laboratory test results and PK data.

Part II: Open, cross-over, food interaction, single-dose study with INDV-2000, which will be given once under fasting conditions and once at completion of a standard FDA high-fat breakfast.

Healthy males (n=8) who meet all eligibility criteria and provide informed consent will receive IMP under fed and fasting conditions. Part II will proceed based upon an acceptable safety evaluation of Part I. The dose studied will be a well-tolerated dose studied in Part I and not exceeding the second highest tolerated dose in Part I.

A schematic depicting the study design is in Figure 1.

Figure 1 Study Schematic- Part I and II



a=active, p=placebo, HV=healthy volunteers; SAD=Single ascending dose

3.1.1 Sample size

The sample size is not based on formal power calculations because the study is designed only to provide an initial assessment of the safety, tolerability and PK of INDV-2000. The sample size used is typical for studies of this nature and should be adequate to assess the parameters described.

3.2 Treatments

The following treatment will be administered.

Part I: IMP will be administered under fasting condition. Subject will fast for at least 10 hrs prior to receiving the IMP. Subjects should be advised to avoid food and liquids other than water for at least 2 hours prior to dosing until at least 1 hour after dosing. Dose per cohort is detailed in Table 2.

[redacted]

Table 2: Part I Single Ascending Dose IMP Dosing

Cohort		1	2	3	4	5
Dose	Active N=6	INDV-2000, 1 mg	INDV-2000, 5 mg	INDV-2000, 20 mg	INDV-2000, 50 mg	INDV-2000, 120 mg
	Placebo N=2	INDV-2000 Placebo, 1 mg	INDV-2000 Placebo, 5 mg	INDV-2000 Placebo, 20 mg	INDV-2000 Placebo, 50 mg	INDV-2000 Placebo, 120mg
Dosage Form (Active; Placebo)	[redacted]					

Cohort		6	7	8	9
Dose	Active N=6	INDV-2000, Dose 6	INDV-2000, Dose 7	INDV-2000, Dose 8	INDV-2000, Dose 9
	Placebo N=2	Placebo, to match	Placebo, to match	Placebo, to match	Placebo, to match
Dosage Form (Active; Placebo)	[redacted]				

Part II: IMP will be administered under fasting conditions in Period 1 and at completion of a standard FDA high-fat breakfast in Period 2. The same INDV-2000 dose will be used for fed and fasted conditions. Dose level is to be determined following Part I.

3.3 Study Procedures

The Schedules of Events for Parts I and II of the study are shown in APPENDIX A.

3.4 Randomization and Unblinding Procedures

Part I of this study will be double-blinded to include the subjects, the Investigator and the Sponsor. [redacted]

[redacted]

The study blind will be broken after the study database has been locked.

3.5 Subject Completion and Subject Replacement

A completed subject is one that has completed the end of study (EOS) visit. Any subject withdrawn or discontinuing the study after being dosed will not be replaced. In Part I, subjects randomized but not dosed will be replaced, and the replacement subject will be assigned the same treatment as the subject being replaced. The study EOS milestone is defined as the last subject's last visit.

3.6 Dose Escalation and Stopping Criteria

3.6.1 Dose Escalation Criteria

Data Review and Safety Committee (DRSC) will review data from cohorts, and will determine if the dose can be escalated, or alternatively if any stopping criteria have been met.

The proposed dose escalation scheme for Part I is described in Table 2, however, a more conservative dose escalation may be explored based on PK, safety and/or clinical observations. Dose escalation factors will be dependent upon observed safety, tolerability and PK, [redacted]

[redacted]

The study will be paused, pending evaluation of all available data by the DRSC, if any of the criteria listed below are fulfilled for an individual dosing cohort:

Adverse Events (AEs):

[redacted]

Laboratory Abnormalities:

[redacted]

Vital Signs:

[redacted]

ECG Criteria:

[redacted]

4 ANALYSIS POPULATIONS

4.1 Safety Population

The Safety population is defined as subjects who received at least one dose of IMP.

4.2 PK Population

The PK population is defined as subjects who received at least one dose of INDV-2000 and have an adequate number of PK samples collected to derive at least one PK parameter. Subjects receiving placebo will not be included in the PK population.

The Food Effect PK population will be defined as the subset of Part II subjects in the PK population that have at least one evaluable PK parameter for at least one meal condition.

[redacted]

5 STUDY SUBJECTS

5.1 Subject Disposition

Subject disposition includes the data of informed consent version, dates of informed consent, completion status (i.e., completed or withdrawn), reason for withdrawal, reasons for screen failure.

A signed written ICF (Informed Consent Form) must be obtained from the subject or a legal representative before any study assessments or procedures may be performed. Informed consent form includes informed consent version visit, informed consent version signed, date of the informed consent signed.

If the subject has permanently discontinued study treatment and is no longer being followed for study assessments and procedures (including follow-up procedures), he/she will be considered withdrawn from the study. The primary reason for withdrawing from the study must be entered into the electronic case report form (eCRF) (e.g., subject is lost to follow-up, Indivior terminates the study or Investigator discretion). Other disposition data will include the date of the randomization, randomization number and cohort information.

Subject must meet all check-in criteria both at screening and at check-in (day -1) before entering into Part I or Part II of the study. The eCRF includes inclusion/exclusion criteria met/not, criteria and comments. A subject will be considered a screen failure if written informed consent was obtained but inclusion/exclusion criteria were not met.

5.2 Protocol Deviations

Protocol deviations will be collected [redacted] PK sampling time deviations will be derived programmatically. Protocol deviations will be identified and documented [redacted]

[redacted]

6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1 Demographic and Other Baseline Characteristics

Demographic data will be collected during the screening of the study. Subject demographics include sex, age, ethnicity and race. Other baseline characteristics include height, weight, and BMI.

6.2 Substance Use Habits

Data will be recorded at the screening visit. Subjects will not be permitted to drink caffeine-containing beverages, eat caffeine-containing foods or use caffeine-containing products prior to check-in through the EOS visit. In addition to 90 days prior to screening, subjects will refrain from smoking and from using e-cigarettes and nicotine-containing products through the EOS visit.

Substance use habits data collection includes category of alcohol (substance use collection date, intake status, quantity of units, and frequency), nicotine (substance use collection date, intake status, quantity of units, frequency, and substance use end date), and xanthine/caffeine (substance use collection date and intake status).

6.3 Medical History

A detailed medical history will be obtained during the screening period. Reported terms will be coded to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA v23.0). Additional information to be collected will include start and end dates and whether the condition is ongoing.

Medical conditions, including surgeries planned before enrolment of the subject in the study, are not considered AEs if the conditions were known before study inclusion and should be reported in the subject's medical history.

Medical history collected during the screening period will include information on the subject's complete history of relevant medical conditions, diagnoses, procedures, treatments and any other noteworthy medical information. Any updates to medical history information made available during the course of the study will be captured.

6.4 Prior Medications

Prior medications are defined as medications taken from signing of informed consent up to time of first IMP dose. Data collected will include medication name, timing, dose, route, frequency, formulation, indication, related AEs and related medical history. Drug classes and standardized names for reported medication names will be coded using WHO-Drug Global September 2020 as defined in the study Data Management Plan (DMP).

6.5 Childbearing Potential

Data on childbearing potential will be collected for female subjects only. Data collected will include collection date, childbearing potential (yes/no), post-menopausal (yes/no), and other reason for non-childbearing potential.

[redacted]

6.6 Standard High Fat Breakfast

Standard high fat breakfast applies only to Part II, Period 2 of the study. Subjects should consume the entire meal in 30 minutes or less, however, the dose must be administered no later than 30 minutes after the start of the meal. Data collected will include meal type, date, time, percent of meal consumed and comment if meal not provided.

[redacted]

7 PHARMACOKINETIC ANALYSIS

The PK analysis will be performed for the PK population. Data listings, summaries, and figures will be done for Parts I and II separately. For Part I, data will be summarized by cohort. For Part II, data will be summarized by condition (fasted and fed).

7.1 Missing Values

The lack of a concentration value due to failure to collect the sample, a lost or compromised sample, or due to the subject's early termination from the study will be termed "missing" in the dataset, and no imputation will be done.

If the actual collection time of a postdose PK sample is inadvertently not recorded (considered as unknown), but a valid concentration value has been measured, the documentation error will be recorded as a protocol deviation, the concentration will be set to missing in the PK analysis and will be presented in listings but excluded from summary statistics.

[redacted]

7.3 Measurements Below the Lower Limit of Quantitation

Concentration values that are below the lower limit of quantitation (BLQ) prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. If two or more consecutive BLQ concentrations are followed by quantifiable concentrations, these quantified values will be set to missing. If a BLQ concentration is followed by a quantifiable concentration, and the quantifiable concentration is then followed by two or more consecutive BLQ concentrations, the quantifiable concentration will be set to missing. The BLQ values following the last quantifiable time points will be set to zero. No concentration estimates will be imputed for missing sample values.

The BLQ rules will be followed for individual and mean PK profile representations and summary statistics, but will be reported as '<LLOQ' in the concentration listings.

7.4 Actual Time

The unknown and duplicate actual time will be managed as per [redacted] SOPs.

The plasma NCA analysis will be based on actual sampling times, except for predose samples, which will be reported as zero, regardless of time deviations provided that they are collected prior to dosing.

The individual plasma concentration-time profiles will be presented by dose level using actual sampling times whereas the mean plasma concentration-time profiles, and tables of summary statistics for concentration-time data will be presented using nominal sampling times.

The actual times will be listed in the report.

7.5 NCA Analysis

The following configuration for the NCA analysis (with Phoenix® WinNonlin® version 8, or higher) will be used:

Data: Serial sampled data

Model/Dose options Type: Plasma (200 - 202) Extravascular

AUC Calculation Method: Linear Up / Log Down (applicable for plasma only)

Lambda $_Z$ (λ_z) calculation: Best fit method for λ_z Linear-Log regression

Reason for exclusion of AUC: In the case where less than 3 consecutive measurable plasma concentrations are observed, the AUC parameters will not be estimated.

The plasma PK parameters requiring λ_z will not be estimated, and will be presented as not calculated (NC), if at least one of the following criteria is not met:

- R^2 >80%
- The terminal phase consists of less than 3 data points or
- $\%AUC_{extrap}$ < 20%

The following PK parameters will be calculated for INDV-2000 and M12:

Table 3: Pharmacokinetic Parameters

Parameter	Definition
C_{max}	Maximum observed plasma concentration
C_{max}/D	Dose-normalized C_{max} (INDV-2000 only)
t_{max}	Time of maximum observed plasma concentration; if the maximum observed concentration is not unique, then the first maximum is used
$AUC_{0\text{-}last}$	Area under the concentration time curve from the time of last dosing to t_{last}
$AUC_{0\text{-}last}/D$	Dose-normalized $AUC_{0\text{-}last}$ (INDV-2000 only)
$AUC_{0\text{-}inf}$	Area under the concentration time curve extrapolated to infinity, calculated as $AUC_{0\text{-}last} + C_{last}/\lambda_Z$, where C_{last} is the measured concentration at time t_{last}
$AUC_{0\text{-}inf}/D$	Dose-normalized $AUC_{0\text{-}inf}$ (INDV-2000 only)
$AUC_{(t1\text{-}t2)}$	Area under the plasma concentration-time curve from t1 to t2 where t1 and t2 represents urine collection interval t1-t2 shorter than the

Parameter	Definition
	scheduled interval of 0-T. Note: This AUC will be estimated to support calculation of CLr over a truncated interval in the event a void is missed during a collection interval resulting in a shorter interval than the scheduled interval from 0-T; otherwise, it will not be estimated
$\%AUC_{extrap}$	Extrapolated area (i.e. percentage of $AUC_{0\text{-}inf}$ due to extrapolation from t_{last} to infinity)
$t_{1/2}$	Plasma terminal elimination half-life, calculated as $\ln(2)/\lambda_Z$
CL/F	Apparent plasma clearance, calculated as Dose/$AUC_{0\text{-}inf}$ (INDV-2000 only)
V_z/F	Apparent volume of distribution, calculated as Dose/ λ_Z * $AUC_{0\text{-}inf}$ (INDV-2000 only)
The following plasma PK parameters will be used for PK calculation and presented in the PK listings only.	
t_{last}	Time of last measurable (positive) observed concentration
R^2	Goodness of fit for the terminal elimination phase
Number of Points	Number of data points in computing λ_Z
λ_z	Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration *versus* time curve
$\lambda_{z\ Upper}$	Upper limit on time for values included in the calculation of λ_z
$\lambda_{z\ Lower}$	Lower limit on time for values included in the calculation of λ_z

[redacted]

7.6 Pharmacokinetic Statistical Methodology

7.6.1 Summary Statistics

Summary statistics of the individual concentration data and derived parameters will be calculated with the built-in Phoenix® WinNonlin® platform and displayed with the same precision as received from the bioanalytical laboratory; additional details on precision rules are provided in Section7.7.

Descriptive statistics will be calculated for INDV-2000 and M12 plasma concentrations for each nominal time point and for all PK parameters, [redacted] Plasma [redacted] individual concentrations and PK parameters obtained from the NCA will be summarized using the following summary statistics: N, minimum (min), arithmetic mean (mean), geometric mean (for main plasma PK parameters only), median, maximum (max), standard deviation (SD), CV%, and geometric CV% (for main plasma PK parameters only).

[redacted]

[redacted]

[redacted]

[redacted]

7.7 Pharmacokinetic Presentation

In general, all PK summary tables will be presented for the PK population.

Individual raw PK concentrations will be displayed with 3 significant digits, unless otherwise recommended.

Precision for individual PK parameters will be displayed as follows:

- C_{max}, AUCs (including dose normalized parameters) and AUC-derived parameters will be displayed with the same precision as the raw PK concentration data
- Parameters associated with time (e.g. t_{max} and $t_{1/2}$) will be displayed with 2 decimal places
- Percentages will be displayed with 2 decimal places

Terminal phase characterization:

- Number of points with 0 decimal place
- R^2 and λ_z with 4 decimal places

Summary statistics for concentration and PK parameters will be displayed with the same precision as the individual values, with the exception of number of observations (N) and coefficient of variation (CV%) which will be presented with 0 and 1 decimal place, respectively.

Concentration profiles will be presented on both linear and semi-log scales. Actual elapsed times of PK plasma sample collection relative to dose administration will be included in the listings.

[redacted]

8 SAFETY ANALYSIS

8.1 Adverse Events

AE monitoring and reporting for each subject will begin after the ICF is signed and will continue throughout the study, including the EOS visit, early termination, and follow-up. Data collected will include reported term, timing, seriousness, severity, toxicity, relationship to IMP, action taken, and outcome. SOCs and PTs for reported terms will be classified using the MedDRA version 23.0 terminology as defined in the study DMP.

8.2 Concomitant Medications

Concomitant medications are defined as medications taken at or after the time of first IMP dose. Data collected will include medication name, timing, dose, route, frequency, formulation, indication, related AEs and related medical history. Drug classes and standardized names for reported medication names will be coded using WHO-Drug Global September 2020 as defined in the study DMP.

8.3 IMP Exposure

IMP administration will be performed on Day 1 in Part I, Part II Period 1, and Part II Period 2. Data collected will include dose, formulation, date/time, route, and whether the subject consumed remainder of 240 mL water, taste masking administered, double rinse was conducted, capsule consumption was verified, and IMP was administered per protocol. For Part II, whether the subject was fasting will also be collected.

8.4 Clinical Laboratory Evaluations

Clinical laboratory data collected will include collection date/time, lab test, result, reference range, out-of-range flag, clinical significance, result and comment.

In the database of laboratory evaluations, results for hematology, chemistry and some urinalysis tests (e.g., specific gravity, pH) will be numeric and results for the remaining urinalysis tests, urine drug screen, serology, and pregnancy tests will be reported as text.

The out-of-range flag will be reported as abnormal, high, low, or normal. Abnormal test results will be further categorized as clinically significant, not clinically significant, repeated, or to be controlled.

The following clinical laboratory tests will be performed according to the schedule in APPENDIX A:

Hematology	**Serum Chemistry:**
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Mean corpuscular hemoglobin	Alanine aminotransferase (ALT)
Mean corpuscular hemoglobin concentration	Amylase
Mean corpuscular volume	Aspartate aminotransferase (AST)
Platelet count	Blood urea nitrogen
Red blood cell count	Calcium
White blood cell count with differential (absolute	

[redacted]

count)

Urinalysis:
Appearance
Bilirubin
Color
Glucose
Ketones
Leucocyte esterase
Microscopic examination of sediment[a]
Nitrite
Occult blood
pH
Protein
Specific gravity
Urobilinogen

Hormone Panel:
Follicle Stimulating Hormone

Pregnancy:
Serum hCG

Screening Only:
Hemoglobin A1c
Hepatitis B surface Antigen
Hepatitis C Antibody
HIV-1 and -2 antibodies
Prothombin Time (PT) with INR
PTT

Carbon dioxide
Chloride
Creatinine
Creatine kinase
Gamma-glutamyl transferase
Glucose (non-fasting)
Lactate dehydrogenase
Lipase
Magnesium
Phosphorus
Potassium
Sodium
Total bilirubin
Direct bilirubin
Total cholesterol
Total protein
Triglycerides

Urine Drug Screen (UDS):
Opioids
Cocaine
Amphetamines
Cannabinoids
Barbiturates
Benzodiazepines
Methamphetamine
Phencyclidine
Ethanol

Anti-HIV = human immunodeficiency virus antibodies; hCG = human chorionic gonadotropin; INR = international normalized ratio; PT = prothrombin time; and PTT = partial thromboplastin time.

[a] Microscopic examination of sediment will be performed only if the results of the urinalysis evaluation are positive (microscopic examination may include but is not limited to White Blood Cell count, Red Blood Cell count, casts and crystals).

[redacted]

8.5 Vital Signs

Vital signs will include SBP, DBP, respiratory rate, heart rate and temperature. Vital signs will be measured according to the schedule in APPENDIX A. Triplicate SBP and DBP measurements will be done at baseline.

8.6 Physical Examination Findings

Physical examination will include date, time and body system examined. Physical examination will be performed according to the schedule in APPENDIX A. At screening, previously unrecognized findings that are clinically significant will be included as adverse events; other clinically significant findings at screening will be included as medical history. After dosing, any new or worsening findings will be included as adverse events.

8.7 Electrocardiogram

12-lead ECG includes the parameter ECG mean ventricular rate, PR interval, QRS duration, QT interval, QTcF interval and interpretation. 12-lead ECGs will be performed according to the schedule in APPENDIX A. Triplicate measurements will be done at baseline. If a potentially clinically significant (CS) abnormality is noted during other time points, a triplicate ECG will be taken at that time point.

ECG holter monitoring will be recorded on Day 1 from at least 2 hours pre-dose until at least 24 hours post-dose for Part I and Part II. The continuous 12-lead ECG data will be stored on secure digital memory cards for potential transfer to a central ECG laboratory as indicated for QT analyses evaluating the risk of prolonged cardiac repolarization. Whether ECG holter monitoring was performed, start date/time, and end date/time will be recorded in the eCRF.

[redacted]

9 DATA HANDLING AND PRESENTATION

All safety and statistical outputs will be generated using SAS software, version 9.4. Pharmacokinetic outputs will be generated using WinNonlin version 8.0 or higher.

The analyses described in this plan are considered *a priori*, in that they have been defined prior to database lock and/or prior to breaking the blind. Any analyses performed subsequent to database lock and/or breaking the blind that are not described within the present plan will be considered post hoc and exploratory. Post hoc analyses will be labeled as such in the corresponding statistical output and identified in the clinical study report (CSR).

9.1 Study Population and Safety Analysis Presentation

Tables of summary statistics will be presented for the Safety population, separately for Part I and Part II. For Part I, summaries will be presented by dosing cohort for active treatment and for all placebo subjects combined; for Part II, summaries will be presented by period. Summary statistics will be number of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables and counts and percentages for categorical variables. For natural log (ln)-transformed endpoints, geometric mean, geometric standard deviation (SD), and coefficient of variation (CV%) will also be presented.

In general, the data listings will include all enrolled subjects and will be presented separately for Part I and Part II. Listings will be sorted by cohort (Part I) or period (Part II) and then by subject.

The following general comments also apply to all statistical analyses and data presentations:

- Study day is defined as (event date–date of first dose) + 1 for event dates on or after the date of first dose, and as (event date–date of first dose) for event dates before the first dose. For Part II, study day will be defined within period.
- Duration will be defined as (end date - start date) +1.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '<10' or '≤5' will be treated as '10' or '5' respectively, and a value such as '>100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.
- If there are multiple assessments for a given nominal visit or time point, the assessment closest in time to the nominal visit or time point will be used in summary tables; if assessments are equidistant from the nominal time point, the mean of the assessments will be calculated and used in summary tables. Assessments classified as "unscheduled" will not be included in summary tables.

In general, summary statistics for raw variables (i.e., variables measured at the study site or central laboratory) will be displayed as follows:

- Minima and maxima will be displayed to the same number of decimal places as the raw data.
- Means, medians, and quartiles will be displayed to 1additional decimal place.

[redacted]

- Standard deviations will be displayed to 2 additional decimal plac
- Percentages will be displayed to 1 decimal place. Percentages between 0 and 0.1 (exclusive) will be displayed as '<0.1'.
- P-values will be displayed to 3 decimal places. P-values that are less than 0.001 will be displayed as '<0.001'.

The numbers of decimal places for summary statistics of derived variables (i.e., variables that are not measured by the study site but are calculated for analysis based on other measured variables) will be determined on a case by case basis. In general:

- Minima and maxima will be displayed to the commonly used unit of precision for the parameter.
- Means, medians, quartiles, and confidence limits will be displayed to 1 additional decimal place.
- Standard deviations will be displayed to 2 additional decimal places.

9.1.1 Subject Disposition

A subject disposition summary will show number of subjects screened, number and percentage of screened subjects randomized (Part I) or enrolled (Part II), number and percentage of randomized (Part I) or enrolled (Part II) subjects who discontinued the study, and reasons for discontinuation with number of discontinued subjects as the denominator. Number and percentage of randomized (Part I) or enrolled (Part II) subjects in each analysis population will also be summarized.

Listings of subject disposition and subjects included in each analysis population will be provided. A listing showing that each randomized (Part I) and enrolled (Part II) subject met all inclusion/exclusion criteria will be provided. Reasons for screen failure will also be listed and summarized.

9.1.2 Protocol Deviations

Protocol deviations and PK sampling time deviations will be provided in separate listings. Protocol deviation listings will include the deviation description, category, and important/not important designation.

9.1.3 Demographic and Other Baseline characteristics

Demographic and other baseline characteristics will be summarized separately for the Safety population, PK populations (if different from Safety population), and screen failures.

9.1.4 Substance Use Habits

Alcohol, nicotine and xanthine/caffeine habits will be presented in listings.

9.1.5 Medical History

Any medical history findings will be presented in listings.

[redacted]

9.1.6 Prior Medications

Prior medications will be presented in listings and will include WHO-DD preferred name, WHO-DD drug class [anatomic therapeutic chemical (ATC) level 2], start and end date/time, dose, route, frequency, and indication. The listing will also include references to related AEs and medical history events, if applicable.

9.1.7 Childbearing Potential

Childbearing potential will be presented in a listing (Part I only).

9.1.8 Standard High Fat Breakfast

Standard high fat breakfast will be presented in a listing (Part II only).

9.1.9 Adverse event

For Part I of the study, a TEAE is defined as an AE with start date/time at or after IMP dosing.

For Part II of the study (a cross-over design):

A Period 1 (Fasted) TEAE is defined as an AE with start date/time at or after IMP dosing in Period 1 and no later than IMP dosing in Period 2.

A Period 2 (Fed) TEAE is defined as an AE with start date/time at or after IMP dosing in Period 2 and within the period of time equal to the interval from Period 1 dosing to Period 2 dosing.

The number and percentage of subjects reporting TEAEs and number of TEAEs will be presented both overall and by MedDRA SOC and PT, each in descending order of frequency (then alphabetically in case of ties). Separate summaries will be done for IMP-related TEAEs, treatment-emergent SAEs (TESAEs), and IMP-related TESAEs. TEAEs will also be summarized by maximum severity and by maximum toxicity grade within SOC and PT (refer to APPENDIX 3 – Tables for Laboratory Abnormalities for events with toxicity grades determined by the protocol); i.e., if more than one TEAE is coded to the same PT for the same subject, the subject will be counted only once for that PT using the most severe event for the summary by maximum severity, and using the most toxic event for the summary by maximum toxicity.

An overall summary table of TEAEs will be provided that shows incidence and number of events for each of the following:

- Any TEAE
- IMP-related TEAE
- TESAE
- IMP-related TESAE
- Severe TEAE
- TEAE with grade 3 or higher toxicity
- TEAE with outcome of study discontinuation
- Fatal TEAE

If any component of an AE starts date/time is missing such that it cannot be determined whether or not the AE was treatment-emergent, it will be counted in summaries as treatment-emergent. In summaries by relationship to IMP and severity, missing relationship will be summarized as "related" and missing severity will be summarized as "severe."

[redacted]

Separate listings will be presented for TEAEs, TESAEs, TEAEs with outcome of study discontinuation, fatal TEAEs, and non-TEAEs.

9.1.10 Concomitant medication

Concomitant medication listings will include the medication name, WHO-DD preferred name, WHO-DD drug class (ATC level 2), start and end date/time, dose, route, frequency, and indication will be presented. The listing will also include references to related AEs and medical history events, if applicable.

9.1.11 IMP Exposure

Details of IMP administration of each subject will be presented in listings.

9.1.12 Clinical Laboratory Evaluations

Laboratory data will be presented using units as reported by the clinical laboratory.

Listings for each category of laboratory test [hematology, serum chemistry, urinalysis, serology, coagulation, urine drug screen and other laboratory tests (pregnancy and endocrinology)] will include test name, study visit, date and time of specimen collection, reference range, observed value, and alert flag. Separate listings will be done for abnormal on-study laboratory values and for CS on-study laboratory values.

Observed values and changes from baseline will be summarized by visit. Shifts from baseline will also be summarized.

9.1.13 Vital Signs

Listings will include study visit, date and time of measurement, and observed value. For baseline SBP and DBP, triplicate measurements as well as the mean of the triplicate measurements will be listed. Separate listings will be done for abnormal on-study vital sign values and for CS on-study vital sign values.

Observed values and changes from baseline will be summarized by visit and time point. Baseline SBP and DBP will be defined as the mean of the triplicate measurements.

Triplicate means will be programmatically calculated and will be calculated even if there are only 1 or 2 measurements available. Triplicate means will be rounded to the nearest integer.

9.1.14 Physical Examination Findings

Listings of general physical examination records and CS physical examination findings will be presented.

9.1.15 Electrocardiogram

Listings will include study visit, date and time of measurement, and observed value. Triplicate measurements as well as the mean of the triplicate measurements will be listed. A separate listing will be done for CS on-study ECGs.

[redacted]

Observed values and, for numeric parameters, changes from baseline will be summarized by visit and time point. Means of triplicate measurements will be summarized for numeric results. ECG interpretation will be summarized by visit, timepoint, and ECG readings.

For numeric parameters, triplicate means will be programmatically calculated and will be calculated even if there are only 1 or 2 measurements available. Triplicate means will be rounded to the nearest integer. For ECG interpretation, if at least 2 of the 3 assessments are the same value, the triplicate summary (analogous to the mean for numeric parameters) will be set to this value; however, if each assessment is different (eg, “normal,” “abnormal NCS,” and “abnormal CS”), the Sponsor will be notified and will provide a value for the triplicate summary of interpretation based on a review of the data.

An ECG holter monitoring listing will include assessment performed, start date/time and end date/time.

[redacted]

9.2 Analysis Timepoints

For Part I, the baseline value will be defined as the last non-missing evaluation prior to the first dose of IMP. For Part II, the period-specific baseline value will be the last non-missing evaluation prior to the first period-specific dose of IMP. If multiple measurements are collected at baseline with the same assessment time (or date if time is not available) then the mean of the measurements will be taken. All other analysis time points will be based on nominal visits.

9.3 Methods for Handling Missing Data

No imputations of values for missing data (ie, blank, “Not Done”, “Not Applicable”, etc) will be performed and data presentations will reflect the data point as it appears in the case report form (CRF) or electronic data file.

[redacted]

10 INTERIM ANALYSES AND DATA SAFETY MONI

In Part I, there will be a review of safety data for the sentinel group in each cohort before proceeding to the next subject in the cohort. There will also be a review of the safety and PK data for each cohort before dose escalation. The safety data review will be conducted by the DRSC using stopping rules defined in Section 3.6.2.

PK parameter estimation for safety review will be performed using bioanalytical data applied with subject aliases in order to maintain the study blind. PK analysis will be performed using nominal time points. The preliminary PK results of INDV-2000 and M12 at the time of the safety review will be performed as outlined in Section 7, with the exception that nominal times will be used in the analysis instead of actual times. Mean concentration-time profiles as well as parameter summary tables of the key PK parameters (e.g. C_{max}, T_{max}, and AUCs) will be generated. [redacted] PK data will not be part of the safety review.

No safety review will be performed for Part II.

[redacted]

11 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

Protocol:	SAP:
The number and percentage of subjects reporting TEAEs will be presented overall, by MedDRA system organ class (SOC) and preferred term (PT), each in descending order of frequency (then alphabetically in case of ties).	Sentence changed to: The number and percentage of subjects reporting TEAEs (incidence) **and number of TEAEs** will be presented both overall and by MedDRA SOC and PT, each in descending order of frequency (then alphabetically in case of ties).
IMP-related TEAEs, treatment-emergent SAEs (TESAEs), IMP-related TESAEs, TEAEs leading to death, TEAEs leading to IMP discontinuation, and TEAEs leading to IMP interruption will be presented both overall and by SOC and PT.	TEAEs leading to death, TEAEs leading to IMP discontinuation, and TEAEs leading to IMP interruption will be listed but not summarized.
TEAEs will also be summarized by intensity within SOC and PT.	Sentence changed to: TEAEs will also be summarized by **maximum severity and by maximum toxicity grade** within SOC and PT
In addition, TEAEs leading to death and IMP-related TEAEs leading to death will be summarized separately by PT	Removed.
	Added: Shifts from baseline in clinically abnormal results will also be summarized.
Concomitant therapies (medications) will be collected from screening until the EOS visit or the ET visit…	Concomitant medications are defined as medications taken at or after the time of first IMP dose.
The PK analysis population is defined as subjects who received at least one dose of INDV-2000 and have an adequate number of PK samples collected to derive PK parameters.	Sentence changed to : The PK population is defined as subjects who received at least one dose of INDV-2000 and have an adequate number of PK samples collected to derive **at least one PK parameter.**
	Added: The Food Effect PK population will be defined as the subset of Part II subjects in the PK population that have at least one evaluable PK parameter for at least one meal condition.

12 GENERAL INFORMATION RELATED TO DATA PRESENTATIONS

The formats and layouts of TFLs are provided in a separate document and are common displays. Their numbering and general content follow the International Conference on Harmonisation (ICH) E3 guidelines. Actual formats and layouts may be altered slightly from those presented as necessary to accommodate actual data or statistics. Minor format changes will not require updates to the SAP, rather they may be documented in a Note to SAP.

[redacted]

13 REFERENCES

Not applicable

[redacted]

APPENDIX A STUDY SCHEDULE(S)

APPENDIX 1 – Schedule of Events Part I

Evaluation	**Screening Days -28 to -1**	**In clinical unit**					**Follow-up**
		Day -1[12]	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 11/EOS[10]/ET**
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Randomization		X					
Demographics (Includes height, weight and BMI)	X						
Medical History	X						
Physical Examination[1]	X	X		X		X	X
Urine Drug Screen	X	X					
Alcohol test	X	X[13]					
Serum Pregnancy Test	X						
Urine Pregnancy Test		X					X
Urinalysis	X	X		X			
FSH test (for post-menopausal women only)	X						
Clinical Laboratory Assessments (Chemistry and Hematology)	X	X		X		X	X
Serology (HIV, Hepatitis B and C)	X						
Coagulation Panel (PT/INR)	X						
Vital Signs[2]	X	X	X[2]	X		X	X
12-Lead Electrocardiogram[3,4]	X[3]	X	X[4]	X		X	X
26 Hour Holter Monitoring[5]			X				
[redacted]							
PK Sampling			X	X	X	X	

[redacted]

Evaluation	Screening Days -28 to -1	In clinical unit					Follow-up
		Day -1[12]	Day 1	Day 2	Day 3	Day 4	Day 11/EOS[10]/ET
[redacted]							
Drug Administration			X				
AE Assessment		X	X	X	X	X	X
Concomitant Medication Assessment	X	X	X	X	X	X	X
Admission to Clinical Unit		X					
Discharge from Clinical Unit						X	

[redacted]

[redacted]

APPENDIX 2 – Schedule of Events Part II

Evaluation		Period 1 - Dosing Under Fasting Condition					Period 2 - Dosing after High-Fat Content Meal					Follow-up
		In clinical unit			Outpatient visits		In clinical unit			Outpatient visits		
	Screening Days -28 to -1	Day -1[11]	Day 1	Day 2	Day 3	Day 4	Day -1[11]	Day 1	Day 2	Day 3	Day 4	Day 10/EOS/ET[9]
Informed Consent	X											
Inclusion/Exclusion Criteria	X	X										
Demographics (Includes height, weight and BMI)	X											
Medical History	X											
Physical Examination[1]	X	X		X			X		X			X
Urine Drug Screen	X	X					X					
Alcohol test	X	X[12]					X[12]					
Urinalysis	X	X		X			X		X			
Clinical Laboratory Assessments (Chemistry and Hematology)	X	X		X		X	X		X		X	X
Serology (HIV, Hepatitis B and C)	X											
Coagulation Panel (PT/INR)	X											
Vital Signs[2]	X	X	X[2]	X		X	X	X	X		X	X
12-Lead Electrocardiogram[3,4]	X[3]	X	X[4]	X			X	X[4]	X			X
26 Hour Holter Monitoring[5]			X					X				
PK Sampling[6]			X[6]	X	X	X		X[6]	X	X	X	

[redacted]

Evaluation	Screening Days -28 to -1	Period 1 - Dosing Under Fasting Condition					Period 2 - Dosing after High-Fat Content Meal					Follow-up
		In clinical unit			Outpatient visits		In clinical unit			Outpatient visits		
		Day -1[11]	Day 1	Day 2	Day 3	Day 4	Day -1[11]	Day 1	Day 2	Day 3	Day 4	Day 10/EOS/ET[9]
Standard High-Fat Breakfast[10]								X				
Drug Administration			X					X[8]				
AE Assessment		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Admission to Clinical Unit		X					X					
Discharge from Clinical Unit				X[7]					X[7]			

[redacted]

[redacted]

APPENDIX 3 – Tables for Laboratory Abnormalities

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN

Cholesterol	201 – 210	211 – 225	> 226	
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade**	**Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.