STATISTICAL ANALYSIS PLAN

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STUDY TITLE: A Randomized, Double-Blind, Single and Multiple Ascending Dose Study to Assess the Safety and Pharmacokinetics of ANA001 in Healthy Adults

PHASE OF STUDY: Phase 1
PROTOCOL NUMBER: ANA001-002
PROTOCOL VERSION/DATE: Version 1.0; 22 October 2020

APPROVALS

Name and Title	Signature	Date
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ABBREVIATIONS

Abbreviation or Special Term	Explanation
AE	Adverse event
ANA	ANA Therapeutics, Incorporated
AUC	Area under curve
BID	Twice daily
BLQ	Below limit of quantification
CL	Clearance
Cmax	Maximum serum concentration
COVID-19	Coronavirus disease of 2019
CV	Coefficient of variation
DMC	Data monitoring committee
FDA	Food and Drug Administration
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non-compartmental analysis
NDA	New drug application
PK	Pharmacokinetic
PT	Preferred term
PVA	Polyvinyl alcohol
SAE	Serious adverse event
SD	Standard deviation
SoA	Schedule of Activities
SOC	System organ class
t1/2	Elimination half-life
TEAE	Treatment-emergent adverse event
TID	Thrice daily
tmax	Time take to reach Cmax
TNF-α	Tumor necrosis factor-alpha
VSS	Volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

The purpose of this plan is to prospectively outline in detail the data derivations, statistical methods and presentations of data so that valid conclusions can be reached to address the study objectives outlined in the protocol ANA001-002, dated 22 October 2020.

The planned analyses identified in this statistical analysis plan (SAP) may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the clinical study report (CSR).

1.1. Responsibilities

Inference, Inc will perform the statistical analyses for all clinical data collected. Inference, Inc is responsible for production and quality control of all tables, figures and listings.

1.2. Timing of Analyses

Data from the SAD Cohorts S1 through S3 will be summarized and evaluated to determine the doses and schedule to be used in a potential fourth SAD cohort and the MAD BID or TID cohorts. Dosing for the potential fourth SAD Cohort S4 will be based on both safety and PK data.

The final analysis will be performed after all subjects complete the study and the database is locked.

1.3. Interim Analysis

The interim analysis based on data from the SAD Cohorts S1 through S3 will be done using aggregate summaries to preserve blinding. The analysis will include listing of safety data, including adverse events. Serious and drug-related adverse events will be taken into in determining the dosing in the MAD part of the study. It may also involve evaluation of laboratory safety data. These analyses will be based on the Safety Analysis.

For evaluating the pharmacokinetics of single dose ANA001, plots of mean (SD) plasma concentration by time will be presented for ANA001 by cohort/dose in linear and semi-logarithmic scales. Pharmacokinetic parameters will also be calculated by each cohort/dose using the methods describes in Section 8, but will use nominal times instead of actual sampling times.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

Primary Objectives:

- To assess safety and tolerability of single oral daily doses of ANA001 (1,000 mg, 2,000 mg and 3,000 mg)
- To assess safety and tolerability of multiple daily oral doses (twice daily [BID] or thrice daily [TID]) of ANA001 for 7 days

Secondary Objectives:

- To assess the PK of single and multiple doses of ANA001

2.2. Endpoints

2.2.1. Primary Outcome Measures

The primary outcome measures are the following safety and tolerability endpoints:

- Incidence of:
  - Treatment-emergent adverse events (AEs)
  - Treatment-emergent serious AEs (SAEs)
  - Study drug discontinuation due to a TEAE (MAD portion only)
- Use of concomitant medications
- Incident of treatment-emergent clinical laboratory tests abnormality
- Change from baseline by visit in:
  - Clinical laboratory tests
  - Vital signs
  - Electrocardiograms (ECG)
  - Physical examinations

2.2.2. Secondary Endpoints

The secondary outcome measures are the following pharmacokinetic endpoints:

- $AUC_{(0\text{-}t)}$
- $AUC_{(0\text{-}last)}$
- $AUC_{(0\text{-}\infty)}$ (SAD only)
- C_{max}
- t_{max}

- $t_{1/2}$
- CL/F
- Vz/F

3. STUDY DESIGN

This is a randomized, double blind study to be conducted in two parts: single ascending dose (SAD) and multiple ascending dose (MAD).

SAD

Eligible participants will be randomly assigned to active drug (ANA001) or placebo in an 8:2 ratio. On Day 1, following an overnight fast of at least 10 hours, participants will receive their assigned treatment (1000 mg, 2000 mg, or 3000 mg of ANA001) with a standardized light meal.

A baseline ECG will be performed at Screening and at 3 hours post-dose. Blood pressure and heart rate will be measured every 8 hours while confined to the clinic. Blood for PK will be collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours post-dose. Participants will be discharged on Day 2 following the 24-hour PK sample and completion of clinical laboratory tests and physical examination. They will return on Day 7 (±2) for follow-up procedures including physical examination, laboratory tests, and assessment of AEs and concomitant medication use.

SAD study design:

Cohort S1: 1000 mg (n=8) or placebo (n=2), single dose
Cohort S2: 2000 mg (n=8) or placebo (n=2), single dose
Cohort S3: 3000 mg (n=8) or placebo (n=2), single dose
Cohort S4: xx mg (n=8) or placebo (n=2) (optional; to be determined)

MAD

Eligible participants will be randomly assigned to active drug (ANA001) or placebo in a 10:2 ratio on a BID (q12h) or TID (q8h) schedule, to be determined based on the PK results of the SAD cohorts. Total daily doses are anticipated to range between 2000 mg and 4500 mg of ANA001. On Days 1 through 7, participants will receive their assigned treatment in the morning with a standardized light meal following an overnight fast of at least 10 hours. Afternoon or evening doses will be given with a light snack. A baseline ECG will be performed at Screening and at 3 hours after the second dose on Day 7. Blood pressure and heart rate will be measured every 8 hours while confined to the clinic.

During BID dosing, blood for PK will be collected on Days 1 and 7 at pre-dose and at 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose. Blood samples will also be collected on Days 2, 4, 6, and 8 at pre-dose and before the 12 hour dose on Days 2, 4, and 6.

During TID dosing, blood for PK will be collected on Days 1 and 7 at pre-dose and at 0.5, 1, 2, 4, 6, and 8 hours post-dose. Blood samples will also be collected on Days 2, 4, 6, and 8 at pre-dose, before the 8 hour dose on Days 2, 4, and 6, and before the 16 hour dose on Day 6.

Participants will be discharged on Day 8 following the last PK sample and completion of clinical laboratory tests and physical examination. They will return on Day 15 (±2) for follow-up

procedures including physical examination, laboratory tests, and assessment of AEs and concomitant medication use.

MAD study design:

Cohort M1: xx mg (n=9) or placebo (n=3) BID or TID for 7 days
Cohort M2: xx mg (n=9) or placebo (n=3) BID or TID for 7 days
Cohort M3: xx mg (n=9) or placebo (n=3) BID or TID for 7 days

3.1. Sample Size Justification

Sample size was not based on statistical considerations. A minimum of 30 participants will be enrolled in the SAD part and up to 36 participants in the MAD part. At least 3 participants of each sex will be included in each cohort.

3.2. Schedule of Activities (SoA)

The following assessments will be performed in this study:

Table 1 Schedule of Activities for SAD

	Screening	In-Patient		Discharge	Follow-up
Study Day	-30 to -2	-1	1	2	7±2
Study PROCEDURES					
COVID PreScreen informed consent	X				
Full study informed consent	X				
Medical history	X				
Prior medications	X				
Physical examination	X				
Abbreviated PE		X	X	X	X
Viral Serology (HIV, HCV, HBV)	X				
Urine alcohol and drug screen	X	X			
Inclusion / exclusion criteria	X	X			
Pregnancy test for WOCBP	X	X			
Randomization		X			
CPU Admission & Confinement		X	X		
CPU Discharge				X	
Drug Administration[a]			X		
Vital signs[b]	X	X	X	X	X
Height	X				
Weight	X	X			
ECG[c]	X		X		
Hematology	X	X		X	X
Serum chemistry	X	X		X	X
Urinalysis	X			X	X
Pharmacokinetics[d]			X	X	
Adverse events		Continuous			
Concomitant medications		Continuous			

WOCBP = woman of child-bearing potential

a.) Administered with Standardized light meal

b.) Blood pressure and heart rate supine for 3 to 5 mins and every 8 hours during CPU confinement

c.) Supine for 5 mins at Screening and 3 hours postdose

d.) 4 mL Predose and 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hr post dose

Table 2 Schedule of Activities for MAD

	Screening	Confinement/Treatment Period								Discharge	Follow-up
Study Day	-30 to -2	-1	1	2	3	4	5	6	7	8	D15±2
Study PROCEDURES											
COVID PreScreen ICF	X										
Full study informed consent	X										
Medical history	X										
Prior medications	X										
Physical examination	X										
Abbreviated PE		X		X			X			X	X
Viral Serology (HIV, HCV, HBV)	X										
COVID Surveillance (ELISA)		+ *Swab*			X			X			
Urine alcohol and drug screen	X	X									
Pregnancy test for WOCBP	X	X									
Inclusion / exclusion criteria	X	X									
Randomization		X									
CPU Admission & Confinement		X	X	X	X	X	X	X	X		
CPU Discharge										X	
Drug Administration[a]			X	X	X	X	X	X	X		
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X										
ECG[c]	X								X		
Hematology	X	X		X			X			X	X
Serum chemistry	X	X		X			X			X	X
Urinalysis	X			X			X			X	X
Pharmacokinetics[d]			X	X	X	X	X	X	X	X	
Adverse events		Continuous									
Concomitant medications		Continuous									

WOCBP = woman of child-bearing potential
a.) Administered with standardized light meal (500 to 750 cal) in AM and light snack (PM) if BID (q12h) or TID (q8h) daily on days 1 through 6 and a single AM dose on day 7
b.) Blood pressure and heart rate supine for 3 to 5 mins and every 8 hours during confinement
c.) Supine for 5 mins at Screening and at 3 hours after second dose on Day 7
d.) see Table 3

Table 3 Schedule of PK Sampling for MAD

	PK Sampling (4 mL) Study Day BID Dosing							
Time (hr)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
PreDose	X[a]	X[a]		X[a]		X[a]	X[a]	X[a]
0.5	X						X	
1	X						X	
2	X						X	
4	X						X	
6	X						X	
8	X						X	
10	X						X	
12	X	X[a]		X[a]		X[a]	X[a]	
	PK Sampling (4 mL) Study Day TID Dosing							
Time (hr)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
PreDose	X[a]	X[a]		X[a]		X[a]	X[a]	X[a]
0.5	X						X	
1	X						X	
2	X						X	
4	X						X	
6	X						X	
8	X	X[a]		X[a]		X[a]	X[a]	

[a] Predose

4. ANALYSIS SETS

Screened participants will be defined as any participant who has signed the ICF. Screened participants who meet all eligibility criteria will be considered enrolled into the study and eligible to receive the single dose of ANA001.

There will be two analysis populations in this study:

Analysis Population	Description
Enrolled	All participants who sign the ICF
Safety Population	All participants randomly assigned to study treatment and who take at any amount of study treatment. Participants will be analyzed according to the treatment they actually received.
Pharmacokinetic (PK) Population	All participants randomly assigned to study treatment, who take at least 1 dose of study treatment, and contribute at least 1 post-dose evaluable PK sample. Participants will be analyzed according to the dose they actually received.

5. GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

5.1. Analysis of the Two Parts

The analyses for the SAD and MAD parts will be presented separately.

5.2. Key Definitions

The Study Day is the day relative to the day of study drug administration (Day 1).

Unless otherwise specified, Baseline is the last non-missing observation before the administration of study drug. The treatment period in both the SAD and MAD parts of the study is defined as Days 1-7 for subjects dosed with study drug.

5.3. Visit Windows and Time Points

There are no plans to derive visit windows, and visits will be used in the analyses as reported on the eCRF.

5.4. Multiplicity Issues

For this early phase study, no multiplicity adjustment will be necessary as no comparisons are being made.

5.5. Subgroup Analyses

Due to the small size of this study, no subgroup analyses are planned.

5.6. Missing Data

For prior and concomitant medication summaries, if the medication start date is completely missing then the medication will be considered both prior *and* concomitant unless it can be determined that the medication end date occurred prior to the study drug administration. If the medication start date is partially missing and the partial date is not sufficient to determine if the medication was taken after study drug administration then the medication will be considered both prior *and* concomitant for the study unless the partial date is clearly after the date of study drug administration (in which case it will be considered concomitant only) or the medication end date is prior to study drug administration (in which case it is prior only).

Completely missing or partially missing adverse event onset dates will be imputed as follows in case due diligence to obtain accurate adverse event information fails:

- If the adverse event start date is completely missing then the adverse event will be considered treatment emergent unless it can be determined that the adverse event end date

occurred prior to administration of study drug. If this is the case, the adverse event will not be considered treatment emergent.

- If the adverse event start date is partially missing and the partial date is not sufficient to determine if the event occurred after the administration of study drug, then the adverse event will be considered treatment emergent unless it can be determined that the adverse event end date occurred prior to the start of the study.

Imputation of missing PK data are detailed in the PK section (section 8.1).

No other missing data will be imputed.

6. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

6.1. Subject Disposition and Populations

Summary tables for subject disposition will be presented for all enrolled subjects, by cohort/dose and overall. The subject disposition summary will contain the numbers of subjects who signed informed consent, failed screening, were randomized, completed the study, and discontinued during the study.

The primary reasons for premature discontinuation during the treatment period will be summarized for the Safety Population.

Number of subjects included in each analysis population will also be displayed.

Listings will be presented on subject disposition and protocol violations.

6.2. Demographic and Baseline Characteristics

All subjects in the Safety Population will be used to summarize the demographic and baseline characteristics with respect to key variables such as age, sex, race, height, weight, and BMI by cohort/dose and overall. Summaries for other variables may be provided if needed.

Continuous variables will be summarized with descriptive statistics: n, mean, standard deviation, median, minimum and maximum value. Categorical variables will be summarized with the number and percentages for each cohort.

Demographic and baseline characteristics such as COVID-19 screening, pregnancy test for WOCBP, urine alcohol and drug, and serology (HIV, HBV, HCV) tests will be listed for each subject.

6.3. Medical History

Medical history including existing diseases will be coded according to the latest version of the MedDRA dictionary. Incidence tables of the number and percentage of subjects by system organ class (SOC) and preferred term (PT) by cohort/dose and overall will be provided for the Safety Population.

Medical history will also be listed by subject.

6.4. Prior and Concomitant Medication

Medications will be separated into prior and concomitant medications. Prior medications are those with start and stop date before the date of study drug administration. Concomitant medications are those with either start date prior to the date of study drug administration and were ongoing while

for the duration of the study *or* those with start date after the date of study drug administration. A medication can be considered both prior and concomitant.

All medications will be coded according to the latest version of the WHO Drug Dictionary and listed by subject. Prior and concomitant medications will be flagged accordingly.

7. PHARMACOKINETIC ANALYSIS

For PK analysis of ANA001, blood samples will be collected during the entire treatment period according to the PK sampling schedules in the SoA. All PK analysis will be based on the PK Population.

7.1. Handling Missing or Non-Quantifiable Data

Below Limit of Quantitation (BLQ) values will be set to zero prior to calculation of descriptive statistics for the plasma concentration-time profile and the log-concentration value will be set to 0 if the value is used in calculating geometric means. Actual elapsed time from dosing will be used to estimate all individual plasma pharmacokinetic parameters. Any anomalous concentration values observed at the pre-dose time point within a period will be examined for the understanding of such an occurrence, and subsequently will result in the exclusion of the subject from the primary AUC analysis, or be assigned a numerical zero for calculating AUC and identified in the CSR.

BLQ value(s) that occur at the beginning of serial sampling (before the first quantifiable concentration value) will be treated as zero, and BLQ value(s) that occur at the end of serial sampling (that is, after the last quantifiable concentration value) will be treated as missing . A BLQ value that is embedded between two quantifiable points will be treated as missing data. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantifiable values will be excluded from the pharmacokinetic analysis by assigning them a value of missing unless otherwise warranted by the concentration-time profile.

7.2. Pharmacokinetic Concentration Analysis

Plasma concentrations of ANA001 will be summarized by cohort/dose and nominal timepoint with descriptive statistics: n, mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum.

Linear and semi-logarithmic plots of the mean plasma concentration by actual sampling time will be provided by cohort. For the MAD part, these plots will be done for both Day 1 and Day 7. Individual subject plots may also be provided for ANA001 in linear and semi-logarithmic plasma concentrations. Additionally, for the MAD part, plots of the trough concentrations by dosing intervals may be plotted to understand the achievement of steady state.

For each part, plasma concentrations of ANA001 at each nominal timepoint will be listed by subject.

7.3. Pharmacokinetic Parameter Analysis

The following PK parameters will be calculated:

- $AUC_{(0-t)}$
- $AUC_{(0-last)}$
- $AUC_{(0-\infty)}$ (SAD only)
- C_{max}
- t_{max}
- $t_{1/2}$
- CL/F
- Vz/F

Actual timepoints will be used for non-compartmental analysis (NCA) calculation.

The area under the curve (AUC) is estimated using linear/log trapezoidal rule with at least three measurable concentrations. For profiles including less than three consecutive measurable timepoints or more than two embedded BLQ values, no AUC will be reported.

Analysis for the SAD Part:

For the SAD part of the study, in calculating $AUC_{0-\infty}$, the terminal elimination phase will be identified by regression analysis using logarithmically transformed plasma concentrations. An elimination phase will be considered invalid for the following situations:

- It has less than 3 data points;
- It has a positive slope (or correlation coefficient [r] > 0);

Adjusted $r^2 \leq 0.8$. (Adjusted $r^2 = 1-\{(1-r^2)\times(n-1)\}/(n-2)$, where n is the number of data points in the regression and r^2 is the square of the correlation coefficient.).PK parameters will be summarized using descriptive statistics (n, mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum) by cohort/dose. Time to maximum concentration, t_{max}, will be summarized by n, minimum, median, and maximum only.

Dose proportionality will be assessed graphically (dose-normalized C_{max} and AUC versus dose). If at least 3 dose groups complete the specific part of the study, dose proportionality in PK parameters may be evaluated by fitting the power model:

$$\log (C_{max} \text{ or AUC}) = \alpha + \beta * \log(\text{dose})$$

An estimate of the slope parameter β and its 90% confidence intervals will be presented.

Individual PK parameters will be listed by subject.

Analysis for the MAD Part:

For both Day 1 and Day 7 in the MAD part of the study, PK parameters will be summarized using descriptive statistics (n, mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum) by cohort/dose. Time to maximum concentration, t_{max}, will be summarized by n, minimum, median, and maximum only.

To understand drug accumulation, geometric mean ratios, and corresponding 90% confidence intervals will be calculated for Day 7/Day 1 for both AUC and Cmax.

For Day 7, dose proportionality may be assessed for steady state C_{max} and AUC using methods similar to those employed for the SAD part of the study.

8. SAFETY ANALYSIS

Safety analyses will be performed on the Safety Population. Safety endpoints include adverse events, vital signs, ECGs, physical examinations, and laboratory examinations (hematology, serum chemistry, and urinalysis).

8.1. Adverse Events

Adverse Events will be coded according to the latest version of the MedDRA dictionary.

In each part of this study, surveillance of adverse events (AE) will begin from the day the subject signs the informed consent form (ICF) until the end of the study.

Adverse events shall be recorded starting at signing of ICF. AEs will be defined as treatment-emergent adverse events (TEAE), if they occurred after initiation of study treatment or if they started prior to study drug administration but worsened after dosing, given that worsening started within the treatment period. All AEs will be listed and flagged as treatment emergent or non-treatment emergent.

Only TEAEs shall be summarized by cohort/dose in the clinical study report. Other AEs will be included in the medical history and will be listed in subject listings.

An overall summary with number and percentage of subjects with all different TEAE categories, like treatment-related, serious, and leading to discontinuation (MAD part only) provided by cohort/dose. Incidence and severity of TEAEs will be summarized by cohort/dose within System Organ Class (SOC), and within Preferred Term (PT).

TEAEs will also be summarized by relationship per SOC and PT. Relationships will be categorized into related (includes “Related” and “Possibly Related”) and unrelated (includes “Not Related” and “Unlikely Related”).

Serious TEAEs and TEAEs leading to discontinuation (MAD part only) will be summarized by cohort/dose with the number and percentage of subjects with treatment-emergent adverse events classified SOC and PT.

All AEs will be listed by subject.

8.2. Clinical Laboratory Assessments

All subjects in the Safety Population will be included in the presentation of the laboratory data.

Clinical laboratory parameters including hematology, biochemistry and urinalyses will be summarized by cohort/dose for each visit. In addition, changes from the baseline visit will be calculated for each visit if baseline and post-baseline measurements are available.

Shift tables may also be used to display the change from before treatment to after treatment measurement with respect to reference ranges “missing”, “low”, “normal”, “high”, and “total”.

All laboratory evaluations, including those that are unscheduled, will be listed by subject, and clinically significant values will be flagged.

8.3. Vital Signs

All subjects in the Safety Population will be included in the presentation of vital signs data.

Vital signs, including the assessments of systolic and diastolic blood pressure, pulse, oral temperature, and respiratory rate, will be summarized by cohort/dose for each visit. In addition, changes from the baseline visit will be calculated for each visit.

All assessments, including those that are unscheduled, will be listed by subject, and clinically significant values will be flagged.

8.4. ECG

All subjects in the Safety Population will be included in the presentation of ECG data.

ECG parameters, including heart rate, QT interval, QTcF interval, QTcF interval, PR interval, and RR interval, QRS interval, will be summarized by cohort/dose for each visit. In addition, changes from the baseline visit will be calculated for each visit.

All assessments, including those that are unscheduled, will be listed by subject, and clinically significant findings will be flagged.

8.5. Physical Examination

All physical examination findings, including those that are unscheduled, will be listed by subject, and clinically significant findings will be flagged.

9. ANALYSIS CONVENTIONS

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation;
2. Date of database lock;
3. SAS®[1] program name, including the path that generates the output;
4. Any other output specific details that require further elaboration.

In general, tables will be formatted with a column displaying findings for all subjects. Row entries in tables are made only if data exists for at least one subject (*i.e.*, a row with all zeros will not appear). The only exception to this rule applies to tables that list the termination status of subjects (*e.g.*, reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

Supportive individual Subject Data Listings will be sorted and presented by cohort, subject number, and visit date, if applicable.

Specific algorithms are discussed for imputing missing or partially missing dates, if deemed appropriate, under specific data topics. Imputed or derived data are flagged in the individual subject data listings. Imputed data will not be incorporated into any raw or primary datasets. The imputed data will be retained in the derived / analysis datasets. Imputation for missing PK data is detailed in the PK section (8.1).

The total duration for a subject *on study* will be calculated as the difference between the date of initial exposure to the study drug and the last day of observation plus one day. All calculations for defining the duration on study will follow the algorithm DURATION = [STUDY COMPLETION OR WITHDRAW DATE – FIRST DOSING DATE + 1].

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- SAD and MAD will be displayed separately – all TLF titles will clearly indicate which part of the study outputs are summarizing.

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n) mean, median, standard deviation (SD), minimum, and maximum values for continuous variables.

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- The number and percentage of responses will be presented in the form XX (XX.X%).

- All summary tables will include the analysis set sample size (i.e., number of subjects).

- Study Day 1 is defined as the first day the subject is exposed to treatment. All study days are determined relative to the day of exposure to the treatment.

- Baseline values will be defined as those values recorded closest to, but prior to, the first study treatment on Day 1.

- Change from baseline will be calculated as follows:

  Change = Post-baseline value – baseline value.

- Date variables will be formatted as DD-MMM-YYYY for presentation.

- SAS® Version 9.4[1] or higher will be the statistical software package used for all data analyses.

- The study treatment, and subject number will be included in all data listings. All listings will be sorted by subject number, visit, visit date, baseline severity, etc. as applicable.

10. REFERENCES

1. SAS Institute Inc., SAS® Version 9.4 software, Cary, NC.
2. Certara USA, Inc. Phoenix® WinNonlin® Version 8.2 software, Princeton, NJ.

11. TABLES, LISTINGS, AND FIGURES

Tables, listings and figures will be listed in a separate Data Displays Document.