Statistical Analysis Plan for Interventional Studies (Early Phase)

Sponsor Name: Crestone, Inc.

Protocol Number: 24-3123-FE/25-0002

Protocol Title: A Phase 1, Single-Center, Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Evaluate the Potential Impact of High-fat Meal on the Pharmacokinetics of CRS3123 200 mg Capsule in Healthy Adult Participants

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Glossary of Abbreviations

Abbreviation	Description
AE	adverse event
ANOVA	analysis of variance
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time zero to infinity (extrapolated)
$AUC_{0\text{-t}}$	Area under the concentration-time curve from time zero until the last observed concentration
BLQ	below the lower limit of quantification
BMI	body mass index
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	confidence interval
Cl/F	Apparent Clearance
C_{max}	maximum observed concentration
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GLM	Generalized linear model
HR	Heart Rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
K_{el}	elimination rate constant
max	maximum
MedDRA®	Medical Dictionary for Regulatory Activities
min	minimum
N	number of participants
n	number of observations
N/A	not applicable
OT	Oral Temperature
PK	pharmacokinetic(s)

Abbreviation	Description
PT	preferred term
p-value	probability value
R^2	R-squared
R^2 adj	R^2 adjusted
RR	Respiratory Rate
SAP	statistical analysis plan
SAS®	Statistical Analysis Software
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
$t_{½}$	elimination half-life
T_{lag}	Time of observation prior to the first observation with a measurable (non-zero) concentration
T_{max}	Time when the maximal concentration is observed
V_z/F	Apparent Volume of Distribution
WHODrug	World Health Organization Global Drug Dictionary

1. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is based on the following documents:

- Protocol 24-3123-FE/25-0002 Final, dated 13-Feb-2025
- Electronic case report form (eCRF) version 1.0, dated 06-May-2-25

The plan may change due to unforeseen circumstances; any changes made after the plan has been finalized will be documented. No revision to the SAP is required for changes which do not affect the statistical analysis methods, definitions, or rules defined in this document. If additional analyses are required to supplement the planned analyses described in the SAP, the changes and justification for the changes will be outlined in the associated clinical study report (CSR). No change will be made without prior approval of the Sponsor.

When applicable, all methodologies and related processes will be conducted according to Syneos Health's standard operating procedures (SOPs), as appropriate. Shells for all statistical tables, listings, and figures referred to in this SAP will be presented in a separate document.

1.1 Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures, and listings (TFLs).

1.2 Timings of Analyses

Final Analysis:

The final safety, tolerability, and pharmacokinetic (PK) analyses will be completed after all participants complete the final study visit or terminate early from the study and after the database lock.

2. Study Objectives

- Primary Objectives:
  - To evaluate the potential impact of high-fat meal on the systemic exposure and the plasma PK of CRS3123 when it is administered as a single oral capsule of 200 mg dose in healthy adult participants
- Secondary Objectives:
  - To evaluate the safety and tolerability of a single oral CRS3123 capsule of 200 mg dose in healthy adult participants
  - To evaluate the plasma PK of the metabolite CRS3123 GLU-3

3. Study Description

This is a Phase 1, single-center, open-label, randomized, single-dose, 2-period, crossover study to evaluate the effect of high-fat meal on plasma PK of CRS3123 200 mg oral capsule in healthy adult participants.

3.1 Subject Selection

Approximately 18 non-smoker, healthy, non-pregnant and non-lactating adults aged 18 to 64 years, with body mass index (BMI) > 18.5 and < 30.0 kg/m^2 and body weight ≥ 50.0 kg for males (as assigned at birth) and ≥ 45.0 kg for females (as assigned at birth), at the time of signing the informed consent, will be enrolled in the study to have at least 16 evaluable participants.

3.2 Determination of Sample Size

The sample size of this study is not determined based on statistical calculations. The proposed sample size of 18 participants is sufficient to achieve the objectives of the study.

3.3 Treatment Assignment

In each period (Day 1 and Day 6), participants will receive one of the following treatments according to the randomization scheme:

Treatment A: A single 200 mg dose of CRS3123 administered orally as 1 x 200 mg capsule (Crestone, Inc., USA) under fasting conditions

Treatment B: A single 200 mg dose of CRS3123 administered orally as 1 x 200 mg capsule (Crestone, Inc., USA) under fed conditions

For Treatment A: No food will be allowed from at least 10 hours before dosing until at least 4 hours after dosing

For Treatment B: After a supervised fast of at least 10 hours, participants will be served a high-fat and high-calorie breakfast. Study drug administration will occur approximately 30 minutes (± 1 minute) after the start of the breakfast.

Table 3.3-1: Crossover Schedule

Treatment Sequence	Period 1	Period 2
AB	A	B
BA	B	A

Treatment A: 1 x 200 mg CRS3123 administered under fasting conditions
Treatment B: 1 x 200 mg CRS3123 administered under fed conditions

3.4 Randomization

This study will be an open-label study due to the objective nature of the data. Participants will be administered each treatment according to the block randomization scheme. Participants will be randomized prior to dosing, after confirming continued eligibility, on Day 1 (Period 1) in a 1:1 ratio (9 per sequence) to one of the 2 treatment sequences, sequence 1: AB or sequence 2: BA.

Randomization schemes will be generated using SAS® for Windows, release 9.4 (SAS Institute Inc., Cary, NC, USA) software, prior to study execution.

Each participant will be randomly assigned a 4-digit randomization number beginning with "1". Each randomization number corresponds to a sequence assignment on the randomization scheme.

3.5 Blinding

Blinding is not applicable since this is an open-label study.

3.6 Participant Withdrawal and Replacement

Participants who withdraw, or are withdrawn, from the study for safety and tolerability reasons after dosing will not be replaced. However, participants who withdraw or are withdrawn from the study prior to dosing, or after dosing for reasons other than safety and tolerability, may be replaced. In such case, the total number of participants dosed will remain within the defined maximum number of participants.

If a participant is replaced, the replacement participant will receive the same treatment assigned to the original participant and will be assigned a randomization number which reflects the original participant's randomization number plus 100 (e.g., a participant assigned to randomization number 1001 would be replaced by a participant assigned to randomization number 1101).

4. Endpoints

- Primary Endpoints:
  - PK Endpoints
    - Area under the concentration-time curve from time zero to infinity (extrapolated) ($AUC_{0\text{-}inf}$), Area under the concentration-time curve from time zero until the last observed concentration ($AUC_{0\text{-}t}$), and Maximal observed concentration (C_{max})
- Secondary Endpoints:
  - PK Endpoints:
    - For CRS3123: Time when the maximal concentration is observed (T_{max}), Time of observation prior to the first observation with a measurable (non-zero) concentration (T_{lag}), elimination half-life ($t_{½}$), elimination rate constant (K_{el}), apparent clearance (Cl/F), and apparent volume of distribution (V_z/F)
    -
    - For CRS3123 metabolite CRS3123 GLU-3: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}, T_{max}, T_{lag}, $t_{½}$, K_{el}
  - Safety Endpoints:
    - Adverse events (AEs), vital signs measurements (blood pressure (BP), heart rate (HR), respiratory rate (RR), and oral temperature (OT)), 12-lead electrocardiogram (ECG) recordings, physical examinations, and clinical laboratory test results, including hematology, biochemistry, and urinalysis

5. Analysis Populations

All participants' inclusion status into each analysis population will be determined after database lock. Participant will be analyzed according to the treatment received in each period.

5.1 Safety Population

The safety population is defined as all participants who receive at least one dose of CRS3123.

5.2 Pharmacokinetic (PK) Population

The PK population will include all participants from the safety population who complete the two periods, and for whom the PK profile can be adequately characterized (at least one primary PK parameter can be estimated for both periods for the comparison).

5.3 Pharmacokinetic (PK) Statistical Population

The PK statistical population will include all participants from the PK population and who have not experienced any significant protocol deviations or other circumstances to exclude the participant from the PK statistical analysis.

A participant with pre-dose concentrations may be excluded from descriptive statistics and analysis of variance (ANOVA) if the pre-dose concentration is greater than 5% of the C_{max} value for that participant.

A participant may be excluded from the descriptive statistics and ANOVA if the participant has experienced emesis within 3 hours of CRS3123 administration.

Data (concentrations and PK parameters) from participants withdrawn due to AEs will be presented but excluded from the statistical analyses (i.e., descriptive statistics and ANOVA).

In addition, any participant with a protocol deviation or AE deemed to affect PK may be excluded from PK populations. Participants may also be excluded from PK populations based upon the following: inclusion and exclusion criteria, acceptable times for visit dates and measurements, compliance with treatment, the nature and quality of the data, withdrawal, and any protocol deviation. Before the final analysis, the pharmacokineticist, in agreement with the Sponsor, will make the final decision of which participants will be included in the PK populations, based on the datasets received.

6. General Aspects for Statistical Analysis

6.1 General Methods

Statistical Analysis Software (SAS®) for Windows release 9.4 (SAS Institute Inc., Cary, NC, USA) software will be used to perform all statistical analyses. All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by participant number, and assessment date/time. The following labels for treatment will be used on all tabulations where the results are displayed by treatment, in the following order:

- Treatment A
- Treatment B

6.2 Summary Statistics:

Unless otherwise stated, continuous variables will be summarized using the number of observations (n), and the statistics mean, median, standard deviation (SD), minimum (Min) and maximum (Max). The min and max values will be presented to the same number of decimal places as recorded in the eCRF, mean and median will be presented to one more decimal place than the raw data, and the SD will be presented to two more decimal places than the raw data.

Summaries of change from baseline variables will include only participants who have both a baseline value and corresponding value at the timepoint of interest. Categorical and binary variables will be summarized with frequency counts and percentages. Percentages will be rounded to one decimal place, with the denominator being the number of participants (N) in the relevant population, unless otherwise stated.

For PK data, values will be rounded to two decimal places in the listings and tables, except for the following situations:

- K_{el} and R-squared (R^2) adjusted data shall be rounded off to four decimal places.

- PK parameters related to time, such as time of maximum observed concentration (T_{max}), T_{lag}, the timepoint at which log-linear K_{el} calculation begins ($K_{el\ Lower}$), and the time of the last observed concentration used to estimate the K_{el} ($K_{el\ Upper}$), must be reported with the same precision as the actual sampling time, rounded to three decimal places.
- Concentration versus time data, as well as maximum observed concentration (C_{max}) shall be reported as they appear in the corresponding dataset.
- Summary statistics, including geometric mean and percentage coefficient of variation (CV%), will be presented to one more decimal place than the raw data. The geometric mean and CV% will not be calculated for T_{max}, T_{lag}, elimination half-life ($t_{½}$), and K_{el}.

Only data from protocol scheduled ("nominal") visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables (unless they were used as baseline) but will be included in the listings and figures.

In the case of a repeat test, both assessments will be presented in the listings. If a repeat measurement was performed due to the first measurement being outside the normal range for the given assessment and the second assessment confirms the first measurement, then only the first measurement will be used for analysis and the second assessment will be considered an unscheduled timepoint. In the same case, if the second assessment falls within normal ranges, then the second assessment will be used for analysis of that timepoint. In all other cases, the first measurement will be taken as the assessment to be used for the analysis.

6.3 Key Definitions

Baseline:

Unless stated otherwise, baseline will be defined for each participant and will be defined as the last non-missing measurement (including repeated and unscheduled assessments) obtained prior to study drug administration for each period. For Period 1, Day 1 pre-dose is considered as baseline and for Period 2, Day 6 pre-dose is considered as baseline. (The Schedule of Assessments and its footnotes in the protocol will be referred to for determining the correct baseline observation.) Post baseline will be considered as all measurements collected after study drug administration. "Unknown", "Not Done", "Not Applicable" and other classifications of missing data will not be considered when calculating baseline observations unless the finding is a valid categorical observation.

Study Day:

Study day will be calculated using the first study drug administration date as the reference date. If the date of interest occurs on or after the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date) + 1. If the date of interest occurs prior to the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date). There will be no study Day 0.

Concomitant Medication:

Concomitant medication is defined as any medication taken by participants after dosing until the last study day and prior medication is defined as any medication taken by participants before dosing.

6.4 Missing Data

There will be no imputation for missing data, unless otherwise specified. Missing data shall be presented in participant listings as either "-" (unknown or not evaluated) or "N/A" (not applicable), with the corresponding definition in the footnotes. Missing descriptive statistics, or probability values (p-values), which cannot be estimated shall be presented as "-".

For inclusion in concomitant medication and AE tables, incomplete start and stop dates on the eCRF will be imputed as follows:

- If the stop date is incomplete, the following rules will be applied:
    - Missing day: Assume the last day of the month
    - Missing day and month: Assume the last day of the year
    - Missing day, month, and year: Assume that the event/medication is continuing
    - In the case of the death of a participant, and if the imputed end date is after the date of death, the end date will be imputed as the date of death
- If the stop date is incomplete, imputed end date will be used instead of reported end date
- If the start date is incomplete, the following rules will be applied:
    - Missing day: Assume the first day of the month; however, if the partial date and the date of the first study drug administration lie within the same month and year and the date of the first study drug administration is not after the stop date of the event/medication, set to the date of study drug administration. Otherwise, set to the stop date of the event/medication.
    - Missing day and month: Assume the first day of the month; however, if the partial date and the date of the first study drug administration lie within the same year and the date of the first study drug administration is not after the stop date of the event/medication, set to the date of the first study drug administration. Otherwise, set to the stop date of the event/medication.
    - Missing day, month, and year: Assume the date of the first study drug administration if it is not after the stop date for the event/medication. Otherwise, set to the stop date for the event/medication.

In the case of withdrawal of consent, all data from participants who withdraw from the study will be included in all summaries up to the time of withdrawal. For all other withdrawals, all data captured will be included in the safety summaries.

For PK analysis, only observed concentration data will be used in the data analysis except for concentration values below the lower limit of quantification (BLQ) as described in 8.1. No attempt will be made to extrapolate or interpolate estimates for missing data.

7. Study Population

7.1 Participant Disposition

The number of participants who were screened, who were enrolled, who were dosed, who completed the study, and who were discontinued from the study, along with reasons for discontinuation, will be summarized by treatment sequence and overall (frequency and the percentage of participants) and presented by participant in a data listing.

7.2 Participant Follow-up

The results of a follow-up call will be listed by participant which include any change in adverse events as well as concomitant medications since last visit/during follow-up period.

7.3 Protocol Deviations

Participant data will be examined for evidence of protocol deviations. All protocol deviations will be categorized and presented by participant in a data listing.

7.4 Inclusion and Exclusion Criteria

All recorded inclusion and exclusion criteria status will be presented by participant in a data listing. Each participant's inclusion or exclusion from each analysis population will also be summarized by treatment sequence and overall (frequency and the percentage of participants) and presented in a data listing.

7.5 Demographics and Other Baseline Characteristics

All demographics and baseline body measurements will be summarized by treatment sequence and overall (frequency and the percentage of participants) and presented by participant in a data listing.

Descriptive statistics (n, Mean, SD, Min, Median, and Max) will be calculated for continuous variables using the last results obtained prior to study drug administration. Frequency counts and percentages will be tabulated for categorical and binary variables.

7.6 Medical History

Medical history will be presented by participant in a data listing. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify medical history terms by system organ class (SOC) and preferred term (PT). Output data will include the MedDRA version used in the study.

7.7 Medications

Prior and concomitant medications will be presented by participant in a data listing. The latest version of the World Health Organization Global Drug Dictionary (WHODrug) will be used to classify medications by anatomical therapeutic chemical (ATC) classification code (2^{nd} level) and preferred name. When a 2^{nd} level classification code is not available, 1^{st} level classification will be used instead. Output data will include the WHODrug version used in the study.

Concomitant medications will be summarized by treatment and overall (frequency and the percentage of participants). This summary will include the percentage of participants with at least one concomitant medication.

7.8 Drug, Cotinine, and Alcohol Screens

The results of drug, cotinine, and alcohol screens will be presented by participant in data listings.

7.9 Pregnancy Screening

The results of pregnancy and follicle stimulating hormone (FSH) tests will be presented by participant in data listings.

7.10 Meal

All data of meal administered to each participant during the study will be presented by participant in data listings.

7.11 Additional Screening Tests

The results of serology tests will be presented by participant in data listings.

8. Pharmacokinetic (PK) Analyses

Phoenix® WinNonlin® software will be used for all PK analyses. Statistical analyses will be performed using SAS for Windows release 9.4 (SAS Institute Inc., Cary, NC, USA) software. The concentrations of all samples should be determined using the validated bioanalytical method prior to the initiation of the PK and statistical analyses.

PK parameter analyses described in this section will be based on the PK population. Statistical analysis described in this section will be based on the PK statistical population. For each analyte, individual and mean plasma concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric means, standard deviation (SD), CV%, Min, Max, and Median) of the plasma concentrations versus time will be presented as well for the PK parameters.

8.1 Data Presentation

PK concentrations will be listed and summarized by nominal sampling time and treatment. For all PK analyses, the concentration values below the quantification limit (BLQ) that occur before the first measurable concentration of the study drug will be set to “0.00”; BLQ values that occur after first measurable concentration will be set to “missing”. No imputations will be made on BLQ concentrations.

Invalid concentration values (due to bioanalytical or clinical issue) that occur prior to dosing will be replaced by “0.00”. Invalid concentration values that occur after dosing will be set to “missing” for tabulation, graphical representation, and calculation purposes.

The actual clock time for dosing and the actual clock time for each PK sample collection will be recorded. For all sampling times, the actual sampling duration will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times, expressed in hours and rounded off to three decimal places, will be used to calculate the PK parameters. Pre-dose sampling times will always be reported as zero (0.000), regardless of the time difference. Nominal sampling times will be used in concentration tables and mean graphs, while actual sampling times for post-dose samples will be used in the individual graphs. Actual sampling times for post-dose samples also will be used for PK parameter derivation, unless the actual sampling time is missing, in which case, the nominal time will be used.

8.2 Pharmacokinetic (PK) Parameters

All PK parameters will be presented in data listings and summarized by treatment, using descriptive statistics (n, arithmetic and geometric means, SD, CV%, Min, Max, and Median).

The following PK parameters will be calculated by standard non-compartmental methods for CRS3123 and/or its metabolite CRS3123 GLU-3.

Table 8.2-1: PK Parameters

Parameter	Definition
AUC_{0-t}	Area under the concentration-time curve from time zero until the last observed concentration
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity (extrapolated)
C_{max}	Maximal observed concentration
T_{max}	Time when the maximal concentration is observed
T_{lag}	Time of observation prior to the first observation with a measurable (non-zero) concentration
$t_{½}$	Elimination half-life
K_{el}	Elimination rate constant
For CRS3123 only:	
Cl/F	Apparent clearance
V_z/F	Apparent volume of distribution

Area under the concentration-time curve (AUC) parameters will be calculated using the linear up log down trapezoidal method, where the linear trapezoidal rule is used any time the concentration data are increasing, and the logarithmic trapezoidal rule is used any time that the concentration data are decreasing. AUC_{0-inf} will be calculated in Phoenix WinNolin as $AUC_{0-t} + C_{last}/K_{el}$, where C_{last} is the last observed quantifiable concentration. The extrapolation of AUC to infinity ($AUC_{\%ex}$) should be $\leq 20\%$. If the $AUC_{\%ex}$ is more than 20%, the individual result depending on AUC_{0-inf} should be flagged. All the derived parameters from AUC_{0-inf}, (i.e., Cl/F, V_z/F) will be flagged accordingly and excluded from the descriptive statistics and statistical analyses.

K_{el} will be the negative of the estimated slope of the linear regression of the ln-transformed plasma concentration versus time profile in the elimination phase. The best fit method in Phoenix WinNolin will be used to calculate the K_{el} from at least three (3) concentration data points, excluding C_{max}. R^2 adjusted (R^2 adj), the goodness of fit statistic for the elimination phase, adjusted for the number of points used in the estimation of K_{el} must be ≥ 0.8. If the R^2 adj is <0.8, the PK parameters derived from K_{el} will be presented in listing(s) but excluded from descriptive statistics in tables. The timepoint where log-linear K_{el} calculation begins ($K_{el\ Lower}$), the actual sampling time of the last measurable concentration used to estimate the K_{el} ($K_{el\ Upper}$), and the R^2 adj for the log-linear regression for the calculation of the elimination rate constant will be reported in listing but not summarize. In addition, $AUC_{\%ex}$ is used for diagnostics and thus listed but not summarized.

Data from CRS3123 GLU-3 will be presented for supportive purpose only.

8.3 Assessment of Food Effect

For CRS3123, using mixed model procedures, ANOVA will be performed on untransformed K_{el} and $t_{½}$ and on ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} at the alpha level of 0.05. Factors incorporated in the model will include sequence, participant (sequence), period, and treatment. Intra and inter-subject coefficient of variation (CV) will be estimated. The ratio of geometric means (B/A) and 90% confidence interval (CI) for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, will be calculated for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}.

The SAS code to perform the test will follow the format below (using the "mixed" Procedure). The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc mixed data= dataset;
      class sequence participant(sequence) period treatment;
      model var = sequence participant(sequence) period treatment / alpha=0.05;
      lsmeans sequence / cl alpha = 0.10;
      estimate 'Treatment B vs Treatment A' treatment -1 1;
run;
```

The clinical relevance of any difference in T_{max} and T_{lag} will also be described. For T_{max} and T_{lag}, a non-parametric analysis of the same comparisons will be performed using a Wilcoxon signed rank test. The median T_{max} and T_{lag} for each treatment and the median of pairwise differences between the fasted and fed treatments (treatment B vs treatment A) will be presented along with the approximate 90% CI.

The SAS code to perform Wilcoxon signed rank test for T_{max} and T_{lag} will follow the format below.

```
proc univariate data=dataset cibasic;
  var Diff_Time;
run;
```

CRS3123 PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max} and T_{max}) values will be plotted against food status. This plot will include individual participant values, and the geometric means (median for T_{max}) for each food status.

8.4 Criteria for Food Effect

No food-effect will be assumed if the 90% CI for the ratio of geometric means (B/A), based on least-squares means from the ANOVA of the ln-transformed CRS3123 $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}, is within 80.00% to 125.00% for CRS3123.

9. Safety

Safety and tolerability analysis will be performed for all participants in the safety population. No inferential statistical analysis of safety data is planned.

9.1 Exposure

Study drug administration will be listed by participant. Exposure will be summarized by treatment and overall.

9.2 Adverse Events (AEs)

Adverse events (AEs) will be coded using the latest version of the MedDRA Version 27.1 SOC and PT. The severity of AEs will be described and documented according to Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007)[d]. Output data will include the MedDRA version used in the study. AEs will be grouped by SOC and PT and summarized by actual treatment. The summary tables will present the number and percentage of total participants and number of events by SOC and by PT.

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), defined as AEs that commence on or after the time of the study drug administration in each study period. AEs without an onset date or time, or AEs with an onset date of the date of the first study drug administration but without an onset time, will be defined as treatment-emergent, unless an incomplete date (e.g., month and year) clearly indicates that the event started prior to the first study drug administration, or the AE stop date indicates that the event started and stopped prior to the first study drug administration.

TEAEs will be attributed to the last treatment administered. TEAEs continuing after dosing in the next treatment period will be evaluated on a case-by-case basis.

The number and percentage of participants experiencing TEAEs and the number of TEAEs will be tabulated. Participants who experience the same TEAE (in terms of PT) more than once will only be counted once at the highest severity and strongest relationship to study drug as per treatment or period, however, the total number of events will be counted per category. This also applies to sub-categories displayed in the summaries.

The following summaries will be presented:

- Overall summary of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship to study drug
- Serious TEAEs by SOC and PT

All AEs will be listed. The following listings will be included: Non-TEAEs, TEAEs, and serious AEs.

9.3 Laboratory Evaluations

Laboratory data, including hematology, biochemistry, and urinalysis, will be listed by participant and summarized by treatment and visit. Observed values and changes from baseline will be presented.

In addition, a shift table representing the categorical change (Grade 1 - Grade 4) from baseline for each treatment at each period to each post baseline visit for the period and the total for each treatment will be presented overall. Grading will be based on Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007)[d] adjusted for the normal range of the laboratory doing the testing. Lab grading as assessed by the Principal Investigator (PI) will be used in the TFL.

Also, a shift table representing the categorical change (abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline visit will be presented overall.

Abnormal results will be flagged in the listings.

9.4 Vital Signs

Vital sign measurements will be listed by participant and summarized by treatment and visit/timepoint. Observed values and changes from baseline will also be presented.

In addition, a shift table representing the categorical change (Grade 1 - Grade 4) from baseline for each treatment at each period to each post baseline visit for the period and the total for each treatment will be presented overall.

Also, a shift table representing the categorical change (abnormal not clinically significant, or abnormal clinically significant) from baseline for each treatment at each period to each post baseline visit for the period and the total for each treatment will be presented overall.

Abnormal results will be flagged in the listings.

9.5 Electrocardiograms (ECGs)

ECG values will be listed by participant and summarized by treatment and visit. Observed values and changes from baseline will be presented.

In addition, a shift table representing the categorical change (Grade 1 - Grade 4) from baseline to each post baseline visit will be presented overall.

Also, a shift table representing the categorical change (abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline visit will be presented overall.

Abnormal results will be flagged in the listings.

9.6 Physical Examination

The results of physical examinations will be listed by participant. Abnormal results will be flagged in the listings.

10. Changes from Analysis Planned in the Protocol

As per protocol, “GLM” procedure was planned for conducting ANOVA. However, ANOVA will be performed using the “mixed” procedure in SAS which will allow inclusion of both fixed and random effects within the model.

The protocol mentions ANOVA as non-parametric test will be performed on untransformed T_{max}. However, in this SAP, T_{max} has been included only for the non-parametric analysis using a Wilcoxon signed rank test. T_{lag} will be included for the non-parametric analysis as well using a Wilcoxon signed rank

test.

11. The study protocol initially required terminal elimination parameters ($t_{½}$ and K_{el}). However, due to low systemic exposure, the terminal elimination phase is unlikely to be characterized and will likely fall within the distribution phase. Consequently, the nomenclature for these parameters has been revised to elimination rate constant and elimination half-life. Programming Considerations

All TFLs and statistical analyses will be generated using SAS for Windows, release 9.4 (SAS Institute Inc., Cary, NC, USA) software in accordance with Food and Drug Administration (FDA) guidelines.

Phoenix® WinNonlin®, version 8.3.4 (Certara USA, Inc., Princeton, NJ) will be used for all PK analyses. This software was validated by Syneos in compliance with United States Code of Federal Regulations (CFR), Title 21, Part 11 (21 CFR Part 11) regulation.

11.1 General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in rich text format that can be manipulated in MS Word.
- Numbering of TFLs will follow International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E3[a] .

11.2 Table, Listing, and Figure Format

11.2.1 General

- TFLs will be produced in landscape format. The orientation may be changed to portrait, as necessary to allow additional rows to be presented.
- TFLs will be produced using the Times New Roman font, size 10. The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all four sides.
- Unless otherwise specified, TFLs will be in black and white (no color).
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used; see below.

- Standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- TFLs will be produced using sentence case, unless otherwise specified.

11.2.2 Headers and Footers

- Times New Roman font, size 10 will be used for TFL headers and footers.
- All outputs will have the following at the top of each page: Crestone, Inc. Protocol 24-3123-FE/25-0002.
- All outputs will have page x of y at the top or bottom right corner of each page. TFLs are individually paginated in relation to total length (i.e., the page number appears sequentially as page x of y, where y is the total number of pages in the output).
- The date and time the output was generated will appear, along with the program name, at the bottom of each page.

11.2.3 Display Titles

Each display title includes the appropriate designation ("Table", "Figure", or "Listing") and a numeral, along with a descriptive name (e.g., Table 14.1-1 Participant Enrollment and Disposition). ICH E3 numbering is strongly recommended, but Sponsor preferences are obtained for final determination. Display titles are left aligned, single spaced, and presented in title case. A solid line spanning the margins will separate display titles from column headings.

11.2.4 Column and Row Headings

- Column and row headings are presented in title case, with the exception of complete sentences, which will be presented in sentence case.
- In safety and PK tables, the variable (or characteristic) column will be on the far left, followed by the group columns and overall column (if applicable). P-values may be presented under the overall column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- Column and row headings will include "Unit" for numeric variables, as appropriate.
- Column and row headings will include the number of participants in the analysis population for each group, presented as (N=xx). This is different from the 'n' used in descriptive statistics, which represents the number of observations.
- The order of treatments in the tables and listings will Treatment A, Treatment B and "overall" (if applicable) last.

11.2.5 Body of the Data Display

11.2.5.1 General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left aligned.
- Whole numbers (e.g., counts) are right aligned.

11.2.5.2 Table Conventions

- Units will be included, where available.
- If the categories of a parameter are ordered, all categories between the maximum and minimum category are presented in the table, even if n=0 for all groups in a category between the minimum and maximum level for that parameter. See the example for the frequency distribution for symptom severity below. If percentages are presented in these tables, 0% will not be presented, therefore, counts of zero will be presented as "0", not "0 (0%)".

Severity Rating	N
Severe	0
Moderate	8
Mild	3

- Where the categories are not ordered (e.g., Reason for Discontinuation), only those categories for which there is at least one participant represented will be included.
- An "Unknown" or "Missing" category will be added to each parameter for which information is unavailable for one or more participants.

- Probability values (p-values) are presented in the format: 0.xxxx, where xxxx is the value. If the p-value is less than 0.0001, it will be presented as "<0.0001." If the p-value is >0.999, it will be presented as ">0.999."
- Percentage values are presented in parentheses with no spaces, one space after the count [e.g., 7 (12.8%), 13 (5.4%)]. Unless otherwise noted, for all percentages, the denominator will be the number of participants in the analysis population for the group that has an observation. Percentages after zero counts are not displayed, and percentages equating to 100% are presented as "100%" (without decimal places).
- Unless otherwise noted, tabular displays of data for medical history, prior/concomitant medications, and AEs data are presented in alphabetical order.
- The percentage of participants is typically calculated as a proportion of the number of participants assessed in the relevant group (or overall) for the analysis population presented; however, careful consideration is required in many instances, due to the complicated nature of selecting the denominator. Details of this will be presented in footnotes or programming notes.
- In categorical summaries where a participant can be included in more than one category, a footnote or programming note will specify whether the participant is included in the summary statistics for all relevant categories or just one category and the criteria for selecting the category.
- Where a category with a subheading (such as SOC) must be split over more than one page, present the subheading followed by "(cont.)" at the top of each subsequent page. The overall summary statistics for the subheading will only be presented on the first relevant page.

11.2.5.3 Listing Conventions

- Unless otherwise noted, listings will be sorted for presentation in order of participant number, visit/collection day, and visit/collection time.
- Dates are printed in SAS DATE9.format (e.g., "ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on participant listings as dashes (e.g.,--JUL2000). Dates that are missing because they are not applicable for the participant are presented as "N/A", unless otherwise specified.
- All observed time values are presented using a 24-hour clock HH:MM:SS or HH:MM format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included, where available.

11.2.5.4 Figure Conventions

- For safety figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values will be displayed on the Y-axis, unless otherwise specified.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- Units will be included, where available.

11.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left aligned, with single spacing, immediately below the solid line beneath the data display.
- Informational footnotes begin with "Note:". Reference footnotes begin with a reference number or letter (e.g., 1, 2, 3 or a, b, c).
- Each new footnote starts on a new line, where possible.
- Participant-specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

12. Quality Control

SAS programs are developed to produce outputs such as analysis data sets, summary tables, data listings, figures, and statistical analyses. These are developed and undergo quality control in accordance with the latest versions of SOP 2800[b] and SOP 2801[c].

13. Reference List

[a]International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (1996). Guideline for Industry, Structure and Content of Clinical Study Reports (ICH E3).

[b]Syneos Health. Standard Operating Procedure, Developing Statistical Programming Specifications for Early Phase Studies (SOP 2800).

[c]Syneos Health. Standard Operating Procedure, Developing Statistical Programs for Early Phase Studies (SOP 2801).

[d]Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. September 2007.

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