Statistical Analysis Plan for Interventional Studies (Early Phase)

Sponsor Name: Aiolos Bio, Inc.

Protocol Number: AIO-001-101

Protocol Title: Open-Label, Single Dose, Parallel Group, Phase 1 Study in Healthy Volunteers Evaluating Safety, Tolerability, Pharmacokinetics, and Immunogenicity of a 400 mg Dose of AIO-001 Administered by Subcutaneous Injection with Two Formulations

Protocol Version and Date: Amendment II and 29 Nov 2023

Syneos Health Project Code: 7053709

Author: PPD Sr Biostatistician

Revision History

Version	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	06 Mar 2024	PPD	Initial draft
0.2	20 Mar 2024		2nd Draft version post sponsor review comments
0.3	04 Apr 2024		3rd Draft version post sponsor review comments
1.0	22 Apr 2024		Final

Approvals

I confirm that I have reviewed this document and agree with the content.

Syneos Health Approval		
PPD Sr Biostatistician		
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
PPD Principal Biostatistician		
Name, Title Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)
PPD Sr Pharmacokineticist		
Name, Title Lead Pharmacokineticist	Signature	Date (DD-Mmm-YYYY)
PPD Mgr, Statistical Prog		
Name, Title Lead Programmer	Signature	Date (DD-Mmm-YYYY)
PPD Medical Writer II		
Name, Title Lead Medical Writer	Signature	Date (DD-Mmm-YYYY)
Aiolos Bio, Inc.Approval		
PPD Director, Statistics		
GSK on behalf of Aiolos Bio, Inc. Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

Table of Contents

Glossary of Abbreviations

Abbreviation	Description
AE	adverse event
ANOVA	analysis of variance
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
$AUC_{0\text{-last}}$	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
CI	confidence interval
C_{max}	maximum observed concentration
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
FSH	follicle stimulating hormone
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
K_{el}	terminal elimination rate constant
K_{el} lower	lower terminal elimination rate constant
K_{el} upper	upper terminal elimination rate constant
Ln	natural logarithm
LS	least squares
max	maximum
MedDRA®	Medical Dictionary for Regulatory Activities
min	minimum
N	number of subjects
n	number of observations
N/A	not applicable
PK	pharmacokinetic(s)
PT	preferred term
p-value	probability value
R^2	R-squared

Abbreviation	Description
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
$T_{1/2\ el}$	terminal elimination half-life
TBD	to be determined
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{max}	time of maximum observed concentration
$T_{½}$.	terminal elimination half-life
vs	versus
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 AIO-001-101 2.0, dated 29 Nov 2023
- Electronic case report form (eCRF) version 3.0, dated 04 Mar 2024

The plan may change due to unforeseen circumstances; any changes made after the plan has been finalized will be documented in the associated clinical study report (CSR). 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 (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

Interim Analysis

An interim analysis will be performed at the end of 12 weeks, after all subjects complete Day 85, safety, tolerability, pharmacokinetic (PK), and immunogenicity data will be analyzed for primary and secondary endpoints for an interim report

Final Analysis

The final safety, tolerability, PK, and immunogenicity analysis will be completed after all subjects complete the final study visit or terminate early from the study.

2. Study Objectives

- Primary objective:
  - To compare the safety and tolerability of 400 mg of AIO-001 as the new formulation (Formulation B) with a 400 mg dose of AIO-001 administered as the original formulation (Formulation A) in healthy volunteers.
- Secondary Objectives:
  - To evaluate the PK of a single subcutaneous (SC) AIO-001 dose of Formulation A in healthy volunteers.
  - To evaluate the PK of a single SC AIO-001 dose of Formulation B in healthy volunteers.
  - To evaluate the immunogenicity of AIO-001 in healthy volunteers.

3. Study Description

This is an open-label single dose, parallel group, 24-weeks, Phase 1 study in 16 heathy subjects.

The study is designed to evaluate and compare the safety, tolerability, PK, and immunogenicity of SC AIO-001 400 mg using two different formulations (original Formulation A and new Formulation B) in 16 healthy volunteers (8 receiving each formulation).

Subject Selection

Up to approximately 16 healthy adult males or females aged 18 to 55 years, with body mass index (BMI) >18.5 and <32.0 kg/m^2, non-smokers, will be enrolled in this study.

3.1 Determination of Sample Size

The proposed number of subjects is in line with the sample sizes commonly used in clinical studies of this nature and is considered sufficient to achieve the study objectives. No formal sample size calculation was performed for this Phase 1 study.

3.2 Treatment Assignment

Sixteen healthy volunteers (8 receiving each formulation) will receive one of the following treatments, according to the randomization scheme. The planned dose levels are listed in Table 3.3-1, below.

Table 3.3-1: Treatments

Group	Number of Subjects	Treatments	Planned Dose
A	8	AIO-001 as Formulation A	400 mg of 100 mg/ml, given as 4 X 1.0 ml
B	8	AIO-001 as Formulation B	400 mg of 182 mg/ml, given as 2 X 1.1 ml

3.3 Randomization

Randomization schemes will be generated using SAS® for Windows software, prior to study execution.

Subjects will be randomized prior to dosing, after confirming continued eligibility. Subjects eligible for participation will be randomized to receive formulation A or formulation B in a 1:1 ratio, for a total of 8 subjects receiving formulation A and 8 subjects receiving formulation B.

The study will include 2 sentinel subjects (1 for each treatment) dosed initially, and the remaining 14 subjects dosed no sooner than 24 hours.

Each subject will be randomly assigned a 4-digit randomization number beginning with "1". Each randomization number corresponds to a treatment assignment on the randomization scheme. Sentinel subjects will be assigned to the first 2 randomization numbers (i.e., 1001, 1002).

3.4 Blinding

This is an open-label study; blinding is not applicable.

3.5 Subject Withdrawal and Replacement

Subjects will be advised that they are free to withdraw from the study at any time. Over the course of the study, the Sponsor and the Investigator or designee may withdraw any subject from the study for one of the reasons described below; subject withdrawal will be done in accordance with the local guidance at the clinical site:

- Safety reason;
- Non-compliance with protocol requirements;
- Significant protocol deviation;
- Positive pregnancy test, drug screen or alcohol breath test.

Subjects who withdraw prior to dosing may be replaced automatically. In the event that the number of dropouts exceeds initial expectations, subjects who withdraw or are withdrawn from the study after dosing, for reasons other than safety and tolerability, may be replaced after consultation between the Investigator and the Sponsor. In such case, the total number of subjects dosed will remain within a maximum of 10 subjects for groups A and B.

4. Endpoints

- Primary Endpoints:
    - Adverse events (AEs), vital sign measurements (blood pressure, heart rate, respiratory rate, and tympanic temperature), 12-lead electrocardiogram (ECG) recordings, physical examinations, and clinical laboratory test results, including hematology, biochemistry, and urinalysis.
- Secondary Endpoints:
    - PK endpoints may include but are not limited to AIO-001 concentrations, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $T_{½}$.

- Incidence of anti-drug antibody (ADA) to AIO-001.

Analysis Populations

All subjects' inclusion status into each analysis population will be determined after database lock. Subjects will be analyzed according to the treatment received.

4.1 Randomized Population

The randomized population will include all randomized subjects. The randomized population will be used for subject listings.

4.2 Safety Population

The safety population is defined as all subjects who receive at least one dose of the study drug.

4.3 Pharmacokinetic Population

The PK population will include all subjects who have at least 1 measured PK concentration following dosing. If any participants have incomplete data, protocol deviations, or clinical events that affect PK, a decision will be made on a case-by-case basis as to their inclusion in the analysis. Before the final analysis, the Pharmacokineticist, in agreement with the Sponsor, will make the final decision of which subjects will be included in the PK populations, based on the datasets received.

4.3.1 Pharmacokinetic (PK) Concentration Population

The PK concentration population will include all subjects who receive AIO-001 and have at least one quantifiable post-dose PK concentration. The PK concentration population will be used for all PK concentration summaries and analyses.

4.3.2 Pharmacokinetic (PK) Parameter Population

The PK parameters population will include all subjects who receive AIO-001 and have sufficient post-dose concentration data to support accurate estimation of at least one PK parameter. The PK parameters population will be used for all PK parameter summaries and analyses.

4.4 Immunogenicity Population

The immunogenicity population will include all subjects who have received any amount of AIO-001 and have at least one post-dose ADA measurement.

5. General Aspects for Statistical Analysis

5.1 General Methods

SAS for Windows 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 treatment, subject 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:

- 400 mg of 100 mg/ml AIO-001 Formulation A

- 400 mg of 182 mg/ml AIO-001 Formulation B

5.2 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 subjects who have both a baseline value and corresponding post baseline 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 subjects (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:

- Terminal elimination rate constant (K_{el}) and R-squared (R^2) adjusted data shall be rounded off to four decimal places.
- PK parameters related to time, such as T_{max}, lower terminal elimination rate constant ($K_{el\ Lower}$), and upper terminal elimination rate constant ($K_{el\ Upper}$), must be reported with the same precision as the actual sampling time, rounded to three decimal places.
- Concentration versus time data, as well as C_{max} shall be reported as they appear in the corresponding dataset.
- Summary statistics, including geometric mean and coefficient of variation (CV%), will be presented to the number of decimal places is contingent on the number of places in the raw data plus one additional decimal place. The geometric mean and CV% will not be calculated for T_{max}, $T_{1/2}$, 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.

5.3 Key Definitions

Baseline:

Unless stated otherwise, baseline will be defined for each subject and will be defined as the last non-analy measurement (including repeated and unscheduled assessments) obtained prior to study drug administration. 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 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.

Prior and Concomitant Medication:

All medications taken by subjects after screening and through to dosing will be documented as prior medications. All medications taken by subjects after dosing through to the last study day will be documented as concomitant medications.

5.4 Missing Data

There will be no imputation for missing data, unless otherwise specified. Missing data shall be presented in subject 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 subject, 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 first study drug administration lie within the same month and year and the date of 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 January 1st; however, if the partial date and the date of first study drug administration lie within the same year and the date of first study drug administration is not after the stop date of the event/medication, set to the date of first study drug administration. Otherwise, set to the stop date of the event/medication.
    - Missing day, month, and year: Assume date of 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 subjects 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). No attempt will be made to extrapolate or interpolate estimates for missing data.

6. Study Population

6.1 Subject Disposition

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

6.2 Protocol Deviations

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

6.3 Inclusion and Exclusion Criteria

All recorded inclusion and exclusion criteria status will be presented by subject in a data listing. Subjects who were screen-failed will not include in this listing. Each subject's inclusion or exclusion from each analysis population will also be presented in a data listing.

6.4 Demographics and Other Baseline Characteristics

All demographics and baseline body measurements will be summarized by treatment and presented by subject 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.

6.5 Medical History

Medical history will be presented by subject 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 26.1.

6.6 Medications

Prior and concomitant medications will be presented by subject 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 (2nd level) and preferred name. When 2nd level classification code is not available, 1st 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 subjects). This summary will include the percentage of subjects with at least one concomitant medication.

6.7 Drug, and Alcohol Screens

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

6.8 Pregnancy Screening and FSH Testing

Pregnancy tests will be administered to females. The follicle stimulating hormone (FSH) level will be tested in postmenopausal females. All results will be presented by subject in data listings.

6.9 Additional Screening Tests

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

7. Pharmacokinetic (PK) Analyses

Phoenix® WinNonlin® software version 8.3.4 (Certara USA, Inc., Princeton, NJ) 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). Bioanalysis of all samples should be completed prior to the initiation of the PK and statistical analyses.

All PK concentration and PK parameter analyses will be conducted on the PK concentration population and PK parameter population, respectively.

PK concentrations will be listed and summarized by treatment, analyte, and nominal sampling timepoint using descriptive statistics (n, mean, SD, CV%, min, max, and median). Individual and mean (±SD) concentration versus time curves will be presented for both linear and semi-log scale by treatment.

7.1 Data Presentation

For all PK analyses, concentration values 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.

7.2 PK Sampling Schedule

A total of 19 blood samples will be drawn from each subject for PK analyses of AIO-001. Specifically, will be collected before (pre-dose) and after dosing on day 1 (12 hours) administration (within 30 minutes) and at, 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 168 hours, 240 hours, 336 hours, 504 hours, 672 hours, 1008 hours, 1344 hours, 1680 hours, 2016 hours, 2688 hours, 3360 hours and 4032 hours post-dose.

7.3 PK Parameters

All PK parameters will be presented in data listings and summarized by treatment and analyte using descriptive statistics (n, arithmetic and geometric means, SD, CV%, min, max, and median).

The PK parameters shown in Table 8.3-1, below, will be calculated by standard non-compartmental methods.

Table 8.3-1: PK Parameters

Parameter	Definition
$AUC_{0\text{-last}}$	area under the concentration-time curve from time zero until the last observed concentration
$AUC_{0\text{-inf}}$	area under the concentration-time curve from time zero to infinity (extrapolated)
Residual area	Percentage of $AUC_{0\text{-inf}}$ due to extrapolation from the time of the last observed concentration to infinity, calculated as [1 - ($AUC_{0\text{-t}}$ / $AUC_{0\text{-inf}}$)] x 100
C_{max}	maximum observed concentration
T_{max}	time when the C_{max} is observed
$T_{1/2\ el}$	terminal elimination half-life, calculated as $\ln(2)/K_{el}$
Kel	Terminal elimination rate constant

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.

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 terminal elimination Phase. The best fit method will be used to calculate the K_{el} from at least three concentration data points, excluding C_{max}. R^2 adjusted, the goodness of fit statistic for the terminal elimination Phase, adjusted for the number of points used in the estimation of K_{el} must be ≥ 0.8. If the $R^2<0.8$, the PK parameters derived from K_{el} will be presented in listing(s) but excluded from descriptive statistics in tables. The timepoint where ln-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 adjusted for the ln-linear regression for the calculation of the elimination rate constant will be reported.

If the Residual area is more than 20%, all the derived parameters depending on $AUC_{0\text{-}inf}$ (i.e., $AUC_{0\text{-}inf}$) will be flagged accordingly.

7.4 PK Comparison Between Formulation A Versus Formulation B

For the PK comparison of the relative bioavailability between formulation A and formulation B, an ANOVA model will be used to compare the log transformed PK parameters $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and C_{max} . The estimated ratio (B/A) of model -adjusted geometric means will be used to perform this comparison. To estimate the geometric mean ratio, a linear mixed effects model will be used to the data. The response variable will be the natural log transformed PK parameter, and the model will include treatment as fixed effect and subject as random effect. The model will be fit using restricted maximum likelihood, and the Kenward--Roger degrees of freedom approximation. From this model, the adjusted means will be estimated for each treatment (A and B). The difference in geometric means will be estimated, accompanied by the corresponding two one-sided 90% confidence interval (CI). The estimates and CIs will be exponentiated using base *e* in order to estimate the geometric mean ratio and associated two one-sided 90% CI..

The SAS code for the analysis model for ANOVA will follow the format given below (using the Mixed Procedure to fit the linear regression). The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc mixed data= dataset;
      class subject treatment;
      model ln_PK_parameter = treatment / ddfm= kr solution;
      random subject;
      lsmeans treatment;
      estimate 'formualtion A vs Formulation B' treatment 1 -1/cl alpha=0.1;
run;
```

8. Immunogenicity Analysis

Anti-AIO-001 antibodies will be evaluated in serum samples collected before and after dosing at 168 hours, 336 hours, 504 hours, 672 hours, 1344 hours, 2016 hours, 3360 hours, and 4032 hours post-dose. The results will be presented in a data listing by subject.

A subject with any ADA is defined as subject with at least one baseline or post-baseline ADA-positive sample. A pre-existing ADA subject is defined as subject who has a baseline ADA-positive sample. ADA-negative subject is defined as subject without treatment-induced or treatment-boosted ADA-positive sample during the treatment or follow-up observation period. ADA-positive subject is defined as subject with at least one treatment-induced or treatment-boosted ADA-positive sample at any time during the treatment or follow-up observation period. Treatment-induced ADA-positive is defined as subject who has baseline ADA-negative sample and at least one post-baseline ADA-positive sample, while treatment-boosted ADA positive is defined as subject who has both baseline and post-baseline ADA-positive samples, and the titer of the post-baseline sample is equal to or more than 4-fold of the baseline titer.

The frequency and percentage of the following information will be summarized; subjects with any ADA, pre-existing ADA subjects, ADA-positive subjects and ADA-negative subject.

All immunogenicity analyses will be conducted on the immunogenicity population.

The frequency and percentage of ADA results will be summarized by treatment and overall.

In addition, the adverse event overview by subject with ADA status will be presented

9. Safety

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

9.1 Exposure

Study drug administration will be listed by subject.

9.2 Adverse Events (AEs)

AEs will be coded using the latest version of the MedDRA. Output data will include the MedDRA version 26.1 AEs will be grouped by SOC and PT and summarized by actual treatment and by overall. The summary tables will present the number and percentage of total subjects 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 study drug administration. AEs without an onset date or time, or AEs with an onset date of the date of 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 administration of study drug, or the AE stop date indicates that the event started and stopped prior to administration of study drug.

The number and percentage of subjects experiencing TEAEs and the number of TEAEs will be tabulated. Subjects who experience the same TEAE (in terms of MedDRA PT) more than once will only be counted once per treatment; 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
- Serious TEAEs by SOC, PT and relationship to study drug

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

9.1 Laboratory Evaluations

Laboratory data, including hematology, biochemistry, coagulation, and urinalysis (quantitative and categorical), will be listed by subject, and summarized by treatment and visit, categorical values less than x or greater than x will be summarized by frequency. Observed values and changes from baseline will be presented.

In addition, a shift table representing the categorical change (normal, abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline visit will be presented by treatment.

Abnormal results will be flagged in the listings.

9.2 Vital Signs

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

In addition, a shift table representing the categorical change (normal, abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline visit and timepoint will be presented by treatment.

Abnormal results will be flagged in the listings.

9.3 Electrocardiograms (ECGs)

Electrocardiogram (ECG) values will be listed by subject and summarized by treatment, visit and timepoint. Observed values and changes from baseline will be presented.

In addition, a shift table representing the categorical change in overall interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline visit and timepoint will be presented by treatment.

Abnormal results will be flagged in the listings.

9.4 Physical Examination

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

9.5 Injection Site Evaluation

The results of injection site evaluation will be listed by subject.

10. Changes from Analysis Planned in the Protocol

Inclusion of the randomized population

11. Programming Considerations

All TFLs and statistical analyses will be generated using SAS for Windows, release 9.4 (SAS Institute Inc., Cary, NC, USA) software. Phoenix® WinNonlin®, version 8.3.4 (Certara USA, Inc., Princeton, NJ) will be used for all PK analysis. This software was validated by Syneos in compliance with US 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: Aiolos Bio, Inc.Aiolos Bio, Inc. Protocol AIO-001-101.
- 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 Subject 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.
- Column and row headings will include "Unit" for numeric variables, as appropriate.
- Column and row headings will include the number of subjects 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 be Treatment A followed by Treatment B, with "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 subject represented will be included.
- An "Unknown" or "Missing" category will be added to each parameter for which information is unavailable for one or more subjects.
- 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 subjects 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 subjects is typically calculated as a proportion of the number of subjects 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 subject can be included in more than one category, a footnote or programming note will specify whether the subject 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 system organ class [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 subject 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 subject listings as dashes (e.g.,--JUL2000). Dates that are missing because they are not applicable for the subject 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.
- Subject-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).

End of document