Statistical Analysis Plan Amendment Final Version 1.0 J1L-AM-JZGF, AM0010-802

An Open Label, Randomized, Single Dose, 3-Way Crossover Study to Evaluate the Pharmacokinetics of Different Dose Levels and Dose Formulations of AM0010 in Healthy Adult Subjects

NCT03381547

Approval Date: 14-Jun-2019

ARMO BioSciences, Inc.

AM0010-802

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14JUN2019

Statistical Analysis Plan Amendment

Final Version 1.0

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List of Abbreviations

AE	adverse event
AUC	area under the serum concentration over time curve
AUC_{0-72}	area under the concentration versus time curve from time 0 to 72 hours
AUC_{0-inf}	area under the concentration versus time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration versus time curve from time 0 to the last observed time point
BLQ	below the limit of quantification
Cl	clearance
CL/F	total body clearance
C_{max}	maximum drug concentration
CSR	clinical study report
CV	coefficient of variation
$DNAUC_{0-72}$	dose normalized area under the concentration versus time curve from time 0 to 72 hours
$DNAUC_{0-inf}$	dose normalized area under the concentration versus time curve from time 0 extrapolated to infinity
$DNAUC_{0-t}$	dose normalized area under the concentration versus time curve from time 0 to the last observed time point
DNC_{max}	dose normalized maximum observed serum concentration
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics

PK	pharmacokinetics
PT	preferred term
SAE	serious adverse event
SAS	statistical analysis software
SD	standard deviation
SOC	system organ class
SQ	subcutaneous
$t_{1/2}$	half life
TEAE	treatment-emergent adverse events
T_{max}	time of maximum concentration observed
Vz/F	volume of distribution

1. Introduction

AM0010 is a PEGylated recombinant form of human IL-10 (PEG-rHuIL-10). AM0010 is produced by prokaryotic fermentation, refolding, purification of rHuIL-10, followed by PEGylation and final purification of AM0010. AM0010 and PEG-rMuIL-10 bind and activate the murine IL-10 receptor in a comparable molar concentration, as shown in cell-based activity assays.

Preliminary evidence obtained in a first in human study with AM0010 administered alone and in combination with chemotherapy suggests that AM0010 is active in multiple tumor types.

In the current study AM0010-802, the pharmacokinetics (PK) of AM0010 at two dose levels (0.4 mg and 0.8 mg for body weight ≤ 80kg / 0.8 mg and 1.6 mg for body weight> 80kg) and two dose formulations (2 mg/mL and 4 mg/mL) will be evaluated. Phase 2 and 3 clinical studies are currently evaluating the efficacy of AM0010 at these dose levels. The formulation currently being administered in ongoing efficacy trials is at a concentration of 2 mg/mL. A high concentration formulation with AM0010 at 4 mg/mL will be introduced into ongoing and future clinical studies. The current study is being conducted to evaluate and to compare the PK of AM0010 at these different dose levels and dose formulation concentrations.

2. Objectives

2.1. Primary

The primary objective of study is to characterize the PK of different dose levels and dose formulations of AM0010 after single subcutaneous (SQ) injections in healthy adult subjects.

2.2. Secondary

The secondary objective is to evaluate the safety of single SQ injections of AM0010 in healthy adult subjects.

3. Investigational Plan

3.1. Overall Study Design and Plan

The study is an open-label, randomized, single dose, 3-way crossover study to evaluate the PK of different dose levels and dose formulations of AM0010 in healthy adult subjects. AM0010 will be the only investigational product used in this study. Two dose levels (0.8 mg and 0.4 mg) and two dose formulations (4 mg/mL and 2 mg/mL) will be evaluated in a 3-way crossover design in 12 subjects. The two dose levels are assigned in two weight brackets, with subjects at or below 80 kg in the lower bracket and subjects with more than 80 kg body weight in the higher bracket.

AM0010 SQ doses of Dose A, Dose B, and Dose C will be administered as indicated in the following table:

Table 3.1.1 Dose levels, Weight Brackets and Formulation of AM0010

Dose	Dose Level		Dose Formulation
	Body weight ≤ 80 kg	Body weight > 80 kg	
A	0.8 mg (0.2 mL)	1.6 mg (0.4 mL)	4 mg/mL
B	0.4 mg (0.1 mL)	0.8 mg (0.2 mL)	4 mg/mL
C	0.4 mg (0.2 mL)	0.8 mg (0.4 mL)	2 mg/mL

Each dose will be separated by 7 days. After each single SQ injection of AM0010, subjects will be followed for 168 hours with PK sampling (serum) and safety evaluations at multiple time points.

Twelve subjects will be randomly assigned in a 1:1:1 ratio to one of three dose sequences:

- A then B then C
- B then A then C

- C then B then A

A schedule of assessments is presented in Table 3.1.2.

Table 3.1.2: Schedule of Assessments

Activities	Screening -28 to -1 Days	Baseline DAYS 0, 7 & 14	DAYS 1, 8 & 15		DAYS 1 - 3 and 8 - 10 and 15 - 17									DAY 21	DAY 22 /EOS
					Hours Post Dose										
			Pre Dose	SQ Injection	2	4	8	12	16	24	36	48	72	168	
GENERAL															
Informed Consent	X														
Clinical Evaluation [a]	X														
Physical Exam	X	X													X
Vital signs [b]	X	X	X												X
12-lead ECG [c]	X														X
Concomitant Medication	●	———	———	———	———	———	———	———	———	———	———	———	———	———	●
Adverse Events Review			●	———	———	———	———	———	———	———	———	———	———	———	●
Confinement at Study Center		●	———	———	———	———	———	———	———	———	———	———	———	●	
Discharged From Unit													After 72 and 168 Hour PK		
LABORATORY ASSESSMENTS AND DOSING															
Hematology	X	X													X
Serum Chemistry	X	X													X

Urinalysis	X	X													X
Urine Drug Screen	X	X												X	
HBV and HCV Serology	X														
HIV 1/0/2 Test	X														
Pregnancy Test [d]	Serum	Urine												Urine	
AM0010 Dosing				X											
AM0010 PK Collection			X		●	—	—	—	—	—	—	—	—	●	

[a] Clinical evaluation will include weight, height, and medical history. Weight measurement (in kg and without shoes) will be obtained at Screening and at the end of the study.

[b] Vital signs (blood pressure, respiratory rate, pulse, and temperature) will be collected after being seated or in a semi-recumbent position for at least 5 minutes.

[c] ECG will be performed in subjects seated, semi-recumbent, or supine for at least 5 minutes.

[d] Serum pregnancy testing in all females.

3.2. Study Endpoints

The primary endpoint is the PK of AM0010; the PK parameters include maximum drug concentration (C_{max}), time of maximum concentration observed (T_{max}), area under the serum concentration over time curve (AUC), Clearance (Cl), half-life ($t_{1/2}$).

The secondary endpoint is the safety of AM0010 including the incidence of adverse events (AEs), clinically relevant changes in laboratory values, and vital signs.

3.3. Dose Adjustment/Modifications

No intra-subject dose adjustments will be allowed.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® software (SAS Institute, Cary, NC USA) Version 9.3 or higher (version to be delineated in the clinical study report [CSR]). All tables and data listings will appear in landscape format employing Courier New 9-point font.

4.1. General Data Presentation Rules

All data will be provided in individual by-subject listings.

Demographic data, baseline characteristics, AEs, laboratory tests, vital signs, and final disposition will be summarized descriptively.

Unless otherwise noted, the summary of the continuous variables will include the number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized descriptively by their counts and associated percentages. Percentages will be calculated using the number of subjects within a summary group as the denominator. No formal significance testing will be performed.

Minimum and maximum values will be presented as the original value. Means and medians will be presented as 1 decimal place greater than the precision of the original value. Standard deviations will be presented as 2 decimal places greater than the precision

of the original value. Percentages for summarizing categorical data will be presented with 1 decimal place. If the percentage value is less than 0.1, then "<0.1" will be displayed.

Unless specified otherwise, baseline will be defined as the last non-missing measurement (including repeated and unscheduled measurements) prior to the first study drug administration.

Listings will be sorted by subject.

4.2. Sample Size

The trial is expected to enroll 12 healthy adult subjects. At least 4 males and 4 females will be enrolled. The sample size is based on practical considerations and is consistent for this type of study.

4.3. Randomization, Stratification, and Blinding

Randomization to one of the three sequences will be based on a randomization schedule prepared by PPD before the start of the study using SAS® software. The subjects will be randomized in a 1:1:1 ratio to one of three doses sequences ABC, BAC and CBA as specified in Section 3.1. At least 4 males and 4 females will be enrolled but there will be no stratification factors. Blinding is not applicable for this open-label study.

In the event subjects are withdrawn before receiving study medication, a replacement subject will be enrolled in the subject's place.

4.4. Repeat/Unscheduled Measurements

For safety summary tables summarized by time point, excluding baseline, if there are repeat measurements for a participant at a scheduled time point, the original measurement at that time point will be used in the summary tables.

Unscheduled results, ie, results that are not from a scheduled event or repeat measurements for a scheduled event, will not be included in the summary tables except for determining baseline, but will be presented in data listings.

4.5. Handling of Missing Data

Subjects with missing data for a particular summary statistic will not be included in the calculation of that statistic but are eligible for inclusion in any other summary statistic for which they provide data. No data imputation algorithm will be used for analysis.

4.6. Analysis Populations

4.6.1. Randomized Population

The randomized population includes all participants who are randomized and will be used for descriptive purposes.

4.6.2. Safety Population

The Safety population includes all participants in the randomized population who received any fraction of AM0010. Safety population will be used for summaries of demographics and safety data. Subjects in the safety population will be analyzed according to the treatment sequence actually received.

4.6.3. Pharmacokinetic Population

The PK population includes all subjects in the safety population who provide sufficient PK data to enable the accurate estimation of at least of at least C_{max} and T_{max}. Subjects with protocol deviations, or who experience dosing or other issues which are deemed to affect the PK data, will be considered for exclusion from the PK population on a case-by-case basis.

5. Subject Disposition

Randomized subjects will be presented in a listing.

Subject disposition data will be presented in a listing. The number and percentage of randomized subjects who completed the study or discontinued the study will be summarized by primary reason of discontinuation for each sequence and overall. Subjects included in each analysis population will be summarized for each sequence and overall.

5.1. Protocol Deviations and Eligibility Criteria Deviations

Protocol deviations will be listed and summarized. Inclusion and exclusion criteria deviations will be listed.

6. Demographics and Baseline Characteristics

6.1. Demographics

Demographic information will be presented in a listing and summarized in a table. Descriptive statistics will be calculated for age (years, calculated as the integer part of [date of informed consent - date of birth]/365.25), screening weight, height, and body mass index. Frequency counts and percentages will be tabulated for sex, race, and ethnicity. The summaries will be presented by sequence (as defined in Section 3.1) and overall for the Safety population.

6.2. Medical History

A complete medical history will be collected including information on the subject's significant past medical events (e.g., prior hospitalizations or surgeries) and any concurrent medical illness. The medical history findings will be presented in a listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Prior and concomitant medication including prescription and non-prescription medications, vitamins, and minerals taken up to 28 days before day 1 and throughout the study, will be collected, coded according to the World Health Organization Drug Dictionary (WHODRUG, version to be delineated in the CSR) and presented in a listing.

7.2. Medical and Surgical Procedures

Medical and surgical procedures data will be presented in a listing.

7.3. Study Treatments

Study drug administration data will be presented in a listing.

8. Safety Analysis

Safety will be assessed by collection and review of AEs, PE findings, vital signs, 12-lead electrocardiogram (ECG) results, and laboratory parameters.

8.1. Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. For analysis purposes, TEAEs are the events with onset on or after initiation of study medication.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version to be delineated in the CSR, by system organ class (SOC) and preferred term (PT).

All summary tables will be based on TEAEs. The SOCs will be displayed in descending order of overall frequency and then alphabetically. The PTs will be displayed in descending order of overall frequency and then alphabetically within SOC. A subject with 2 or more AEs within the same level of summarization will be counted only once in that level using the most severe (for the severity table) or most related (for the relationship to study drug table) incident.

Summary tables will be presented by dose, meaning the most recent dose A, B or C before the AE onset. Percentages will be based upon the number of subjects in the safety population overall and within each dose.

8.1.1. Incidence of Adverse Events

All AEs will be presented in a data listing, and all TEAEs will be presented in a summary table by SOC, PT and the most recent dose (A, B, C) and overall.

An overall summary table will be created presenting the number and percentage of subjects with:

- Any TEAE
- Any treatment-related TEAE
- Any TEAE of severity grade greater than 3
- Any treatment-related TEAE of severity grade greater than 3
- Any serious adverse event (SAE)
- Any treatment-emergent, treatment-related SAE
- Any AE leading to early study discontinuation
- Any death

8.1.2. Relationship of Adverse Events to Study Drug

The relationship of AE to study drug will be classified by the Investigator as related or not related. If the relationship information is missing on the eCRF, then the AE is considered as related in the summary. TEAEs will be summarized by relationship (related, unrelated), SOC, PT and dose (A, B, C and overall). A subject with 2 or more TEAEs within the same level of summarization will be counted only once in that level using the most related incident.

8.1.3. Severity of Adverse Event

The severity of AEs will be assessed by the Investigator using ‘Grade 1’– ‘Grade 5’ scale as defined in the Common Terminology Criteria for Adverse Events v 4.03 (CTCAE: National Cancer Institute) grades. The TEAEs will be summarized by SOC, PT, severity

(including category 'Missing' for events with missing severity assessment on eCRF) and by the most recent dose (A, B, C) and overall. A subject with 2 or more TEAEs within the same level of summarization with at least 2 different non-missing severity grades will be counted only once using the highest severity grade.

8.1.4. Adverse Events Leading to Early Discontinuation

All AEs that lead to early discontinuation will be presented in a listing.

8.1.5. Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose (including after informed consent is given and prior to dosing) that results in any of the following outcomes:

- Death
- Life threatening event (results in an immediate risk of death from the reaction as it occurred)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

All SAEs including deaths will be presented in a data listing.

8.2. Clinical Laboratory Evaluations

Blood samples for local laboratory safety tests (chemistry and hematology) and urine samples for urinalysis will be collected at screening, day 0, day 7, day 14 and day 22/end of study (EOS).

Serum Chemistry includes: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, amylase, total protein, albumin, calcium, magnesium, and phosphate.

Hematology includes: red blood cell count, white blood cell count, hemoglobin, hematocrit, reticulocyte counts, platelet count, differential, neutrophils, lymphocytes, and monocytes.

Urinalysis includes: specific gravity, pH, blood, protein, glucose, ketones, bilirubin, urobilinogen, white blood cells, red blood cells, epithelial cells, bacteria, casts, and crystals

Urine microscopic evaluation will only be performed if an abnormal urine dipstick result is observed.

Urine samples for urine drug screen will be collected at screening, day 0, day 7, day 14 and day 21 and the drugs to be screened for include: amphetamine, cocaine, opiates, benzodiazepines, barbiturates, methadone, alcohol/ethanol, and cannabinoids.

Virology testing will be performed at screening and includes: anti-HCV antibody, hepatitis B surface antigen, and HIV 1/0/2 Testing.

For all female subjects, serum pregnancy test will be performed at screening and urine pregnancy test will be performed at day 0, day 7, day 14 and day 21.

The hematology, chemistry, and urinalysis test results will be presented in the data listings sorted by subject, laboratory test, and sample collection date/time. Values that are outside of the normal range will be flagged in the listings. Actual results and change from baseline will be summarized for the safety population. Refer to Section 4.1 for the definition of baseline for this summary.

All other laboratory tests will be presented in a data listing sorted by subject, laboratory test category, laboratory test, and sample collection date/time.

8.3. Vital Sign Measurements

Vital signs including blood pressure, respiratory rate, pulse, and temperature will be collected after being seated or in a semi-recumbent position for at least 5 minutes at screening, day 0, day 1 (predose), day 7, day 8 (predose), day 14, day 15 (predose), day

22/EOS and at early termination. Any abnormal measurements may be repeated and reported as AEs, if appropriate.

Vital signs results will be presented in a data listing sorted by subject, and collection date/time. Actual results and change from baseline will be summarized for the safety population. Refer to Section 4.1 for the definition of baseline for this summary.

8.4. Electrocardiogram

Single 12-lead ECGs including, Heart Rate, PR Interval, QRS Duration, QT Interval, QTcF Interval and overall interpretation will be obtained at screening, day 22/EOS and at early termination. Subjects will be seated, semi-recumbent, or supine for at least 5 minutes before the ECG is obtained. ECG results will be presented in data listing sorted by subject, treatment sequence, and date/time of assessment. Actual results and change from baseline will be summarized for the safety population. Refer to Section 4.1 for the definition of baseline for this summary.

8.5. Physical Examination and Physical Measurements

Physical examination will be performed at screening, day 0, day 7, day 14, day 22/EOS and at early termination. Physical examination data will be presented in a listing sorted by subject, date/time of assessment and body system.

Weight will be measured at screening, day 0, day 22/EOS and at early termination and presented in a listing sorted subject, and date/time of assessment.

Screening height and weight will be listed and summarized together with demographics variables.

9. Pharmacokinetics

9.1. Serum Pharmacokinetic Concentrations

Serial blood samples for PK assessment of AM0010 will be collected at the following time points:

Period	Day(s)	Timepoints
1	1-3	Predose, 2, 4, 8, 12, 16, 24, 36, 48 and 72 hours after Dose 1
2	8-10	Predose, 2, 4, 8, 12, 16, 24, 36, 48 and 72 hours after Dose 2
3	15-17 and 22	Predose, 2, 4, 8, 12, 16, 24, 36, 48, 72, and 168 hours after Dose 3

Individual serum concentrations, dose normalized serum concentrations, actual sampling times and time deviations of AM0010 will be listed using the safety population (concentration data will be presented to the same precision as the raw data). Individual serum concentration and dose normalized serum concentrations versus actual time profiles will be plotted showing the selections for the terminal elimination rate constant for each subject using the Safety population.

The following descriptive statistics for individual AM0010 serum concentrations, dose normalized AM0010 serum concentrations will be provided for each body weight category, dose and sampling time used for the PK analysis (Days 1 and 8 at zero to 72 hours postdose and Day 15 at zero to 168 hours post dose) using the PK population: n, arithmetic mean, arithmetic SD, CV, median, minimum and maximum. Mean serum concentration versus nominal time profiles will be plotted, where possible, using the PK population.

Samples collected outside the allowable window (±10% of the protocol time) will be flagged and excluded from the calculation of summary statistics. Mean serum concentrations and dose normalized serum concentrations will be plotted versus nominal time, and individual whole blood concentrations and dose normalized serum concentrations will be plotted versus actual time, on both linear and semilogarithmic scales.

For the calculation of summary statistics, all values that are below the limit of quantification (BLQ) will be treated as zero.

9.1.1. Values Below the Limit of Quantitation or Missing

Concentration values that are below the BLQ will be set to zero, with defined exceptions as follows:

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a predose concentration is missing, these values will be set to zero.

9.1.2. Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in PK section of the CSR.

Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

Where the predose value for a subject is greater than 5% of the C_{max}, all values and PK parameters will be listed, flagged and included in the PK summary tables. Where the predose value for a subject is greater than 10% of the C_{max} for a subject, all values and PK parameters will be listed, but the associated value will be excluded from the concentration summaries, and the associated PK parameters will be excluded from the summary statistics.

If required, a sensitivity analysis will be carried out to assess the impact of any predose value greater than 10% on the Day 1 PK parameters.

9.2. Serum Pharmacokinetic Parameters

The following serum PK parameters will be estimated for AM0010 via non-compartment analysis using Phoenix WinNonlin version 6.4 or higher (version to be delineated in the CSR):

C_{max}	Maximum observed serum concentration
DNC_{max}	Dose normalized maximum observed serum concentration, calculated as C_{max} divided by dose in mg
T_{max}	Time of the maximum observed serum concentration
AUC_{0-72}	Area under the concentration versus time curve from time 0 to 72 hours (i.e. the last sampling time in common across all three doses), calculated using the linear up log down trapezoidal rule
$DNAUC_{0-72}$	Dose normalized area under the concentration versus time curve from time 0 to 72 hours, calculated as AUC_{0-72} divided by dose in mg
AUC_{0-t}	Area under the concentration versus time curve from time 0 to the last observed time point with a concentration above the lower limit of quantification, calculated using the linear up log down trapezoidal rule
$DNAUC_{0-t}$	Dose normalized area under the concentration versus time curve from time 0 to the last observed time point, calculated as AUC_{0-t} divided by dose in mg/kg
AUC_{0-inf}	Area under the concentration versus time curve from time 0 extrapolated to infinity, calculated as AUC_{0-inf} divided by dose in mg
$DNAUC_{0-inf}$	Dose normalized area under the concentration versus time curve from time 0 extrapolated to infinity, calculated as AUC_{0-inf} divided by dose in mg
$t_{1/2}$	Apparent terminal elimination half-life, calculated as [(ln 2)/Kel]. If the length of the time interval used to determine Kel is less than 2 times $t_{1/2}$,

then $t_{1/2}$ will be flagged (i.e., $t_{1/2}$ values that are more than half the time interval used to determine Kel will be flagged).

CL/F — Total body clearance, calculated as: Dose / $AUC_{0\text{-inf}}$

Vz/F — Volume of distribution, calculated as: CL/F / Kel

In addition to the above PK variables, which will be listed and summarized, the following parameters will also be listed to document the selection of data points used to estimate $t_{1/2}$ using non-compartmental procedures:

Kel — Terminal elimination rate constant; the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase

Npts — Number of data points used to estimate Kel; a minimum of 3 data points must be used, and C_{max} must not be included

Kel_lower — Lower bound used for the estimation of Kel

Kel_upper — Upper bound used for the estimation of Kel

Adjusted Rsq — The coefficient of determination (goodness of fit statistic) adjusted for Npts; Kel will only be retained if adjusted $r^2 \geq 0.80$.

%AUCext — Percentage of AUC extrapolated from the last quantifiable concentration to infinity; AUC0-inf will be listed, flagged and included in the summary statistics when %AUCext is greater than 20% but less than 30%, AUC0-inf will be listed but excluded from summary statistics when %AUCext is greater than 30%.

Actual PK blood sampling times will be used for the assessment of all PK parameters.

Individual serum PK parameters of AM0010 will be listed and summarized by body weight category and dose using the PK Population. The following descriptive statistics will be provided for all PK parameters, with the exception of T_{max} and $t_{1/2}$, at each dose level using the PK Population: n, geometric mean, geometric coefficient of variation (geometric CV),

arithmetic mean, arithmetic SD, arithmetic CV, median, minimum and maximum. The parameter Tmax will only be summarized using n, median, minimum and maximum, and $t_{1/2}$ will only be summarized using geometric mean and CV; n, minimum, maximum, and median.

To assess the effect of different dose levels and dose formulations, ping-pong plots of DNC_{max}, $DNAUC_{0\text{-}72}$, $DNAUC_{0\text{-}t}$ and $DNAUC_{0\text{-}inf}$ will be created comparing Dose A and B for the effect of dose and Dose B and C for the effect of formulation. Both the individual PK parameter values and geometric mean values will be displayed on the linear scale for each dose and treatment.

For the listings, concentration data will be presented to the same precision as the data is received. All PK parameters will be presented in the listings to 3 significant figures with the exception of Tmax, which will be presented to 2 decimal places.

For summary statistics, the following precisions should be used:

- n should be presented to zero decimal places.
- Geometric CV and CV should be presented to zero decimal places.
- Geometric mean, Mean, SD, median, minimum, and maximum should be presented to the same precision as the listings.

9.3. Pharmacokinetic Statistical Analyses

No formal statistical analysis is required for this study.

9.4. Population PK Analyses

If required, full details of the population PK modelling analysis will be specified in a separate analysis plan.

10. Interim Analysis

No interim analysis is anticipated for this study.

11. Table of Contents: Tables, Listings and Figures

List of Tables

Subject Disposition

Table 14.1.1. Subject Disposition (Randomized Population)

Demographics and Baseline Characteristics

Table 14.1.2 Subjects with Protocol Deviations/Violations by Treatment (Safety Population)

Table 14.1.3 Demographic and Baseline Characteristics (Safety Population)

Pharmacokinetics

Table 14.2.1 Summary of Serum Concentrations of AM0010 (PK Population)

Table 14.2.2 Summary of Dose Normalized Serum Concentrations of AM0010 (PK Population)

Table 14.2.3 Summary of Serum Pharmacokinetic Parameters of AM0010 (PK Population)

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Statistical Analysis Plan (SAP) Client Approval Form

Client:	**ARMO Biosciences, Inc / Eli Lilly and Company**
Protocol Number:	**AM0010-802**

Document Description:	Final Statistical Analysis Plan Amendment
SAP Title:	An Open Label, Randomized, Single Dose, 3-Way Crossover Study to Evaluate the Pharmacokinetics of Different Dose Levels and Dose Formulations of AM0010 in Healthy Adult Subjects
SAP Version Number:	1.0
Effective Date:	14 JUN 2019

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