

Statistical Analysis Plan (V2): J1L-AM-JZGE/AM0010-801

A Phase 1 Study to Evaluate the Pharmacokinetics of Single and Multiple Doses
of AM0010 in Healthy Adult Subjects

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ARMO Biosciences, Inc.

AM0010-801

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Doses of AM0010 in Healthy Adult Subjects**

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Final Statistical Analysis Plan

Version 2.0

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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

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Listing of Abbreviations

Abbreviation	Definition
%AUCext	percentage of AUC extrapolated the last quantifiable concentration to infinity
AE	adverse event
AM0010	PEGylated recombinant human interleukin 10
AUC0-24	area under the concentration versus time curve from time 0 to nominal 24 hours post-dose
AUC0-inf	area under the concentration versus time curve from time 0 extrapolated to infinity
AUC0-t	area under the concentration versus time curve from time 0 to the last observed time point
AUC0-tau	area under the concentration versus time curve within a dosing interval (i.e. 24 hours)
AUEC0-24	area under the effect versus time curve from time 0 to nominal 24 hours postdose
BLQ	below the limit of quantification
CL/F	total body clearance
Cmax	maximum serum concentration
Ctrough	trough (predose) serum concentration
CSR	clinical study report
CV	coefficient of variation
eCRF	electronic case report form
EKG	electrocardiogram
Emax	maximum effect
EOS	end of study
ET	early termination
HR	heart rate
Kel	terminal elimination rate constant
MedDRA	medical dictionary for regulatory activities
n	number of subjects
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PopPK	population PK
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAAUC	accumulation ratio for AUC
RACmax	accumulation ratio for Cmax
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SQ	subcutaneous
t _{1/2}	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TEmax	time of maximum effect

Abbreviation	Definition
tmax	time of the maximum serum concentration
Vz/F	volume of distribution
WHODrug	World Health Organization Drug Dictionary

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.

In the current study AM0010-801, the pharmacokinetics (PK) of AM0010 at two dose levels (5 µg/kg and 10 µg/kg) will be evaluated. Based on an interim PK analysis from the First-in-Human study AM0010-001, apparent clearance varied as a function of dose. In this clinical study, doses up to 40 µg/kg were safe and well-tolerated. In addition, dose levels between 5 µg/kg and 20 µg/kg have been associated with clinical activity in patients with advanced solid malignancies. Because these dose levels will be used in the Phase 3 program, detailed evaluation of the PK of AM0010 at 5 µg/kg and 10 µg/kg are warranted.

2 Objectives

2.1 Primary Objectives

The primary objective is to characterize the PK of AM0010 after single and multiple subcutaneous (SQ) injections in healthy adult subjects.

2.2 Secondary Objective

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

3 Investigational Plan

3.1 Overall Study Design and Plan

The study is an open-label, single followed by multiple dose study to evaluate the PK/ pharmacodynamic (PD) of AM0010 in healthy adult subjects. Subjects will receive a single SQ injection of AM0010 and be followed for 72 hours with PK (serum) sampling at multiple time points. Subjects will then receive AM0010 at the assigned dose SQ once daily × 6 and have PK samples collected at multiple time points between injections as well as after the final injection of AM0010. Two dose levels (5 µg/kg and 10 µg/kg) will be evaluated with 12 subjects enrolled at each dose level.

Twenty-four subjects will be randomly assigned in a 1:1 ratio to 2 dose levels of AM0010 (5 µg/kg and 10 µg/kg). AM0010 at 5 µg/kg will be administered as one of 2 fixed doses (i.e., either 400 µg in 200 µL for body weights ≤ 80 kg or 800 µg in 400 µL for body weight > 80 kg) based on the subject's weight during the course of the study. AM0010 at 10 µg/kg will be administered as one of two fixed doses (i.e., either 800 µg in 400 µL for body weights ≤ 80

kg or 1600 µg in 800 µL for body weight > 80 kg) based on the subject's weight during the course of the study.

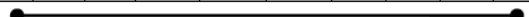
Table 4.1.1 AM0010 Dosing

ARM	Dose Level	Concentration	Subject Weight	Dose and Volume AM0010
1	5 µg/kg	2 mg/mL	≤80 kg	400 µg in 0.2 mL
			>80 kg	800 µg in 0.4 mL
2	10 µg/kg	2 mg/mL	≤80 kg	800 µg in 0.4 mL
			>80 kg	1600 µg in 0.8 mL

Subjects will be admitted to an inpatient research facility on Day 0 and remain in residence from Day 0 to Day 12. On Day 0, baseline procedures including physical examination, safety laboratory tests, vital signs, electrocardiogram (EKG), and serum pregnancy (in all females) will be performed. Prior to dosing on the morning of Day 1, a sample for PK/PD will be drawn prior to dosing, and subjects will then receive a SQ injection of AM0010. On the morning of Days 4 through 9, subjects will receive a SQ injection of AM0010 at the same dose that was administered on Day 1.

The subjects will be discharged from the inpatient research facility on the morning of Day 12 after completion of study-related procedures. The Day 15 End-of-Study (EOS) visit to the research site will be on an outpatient basis for, safety assessments, and safety blood draw time points outlined in the Schedule of Events [Table 4.1.2](#).

Table 4.1.2 Schedule of Study Events

Activities	Screening -28 Days	Baseline Day 0	DAY 1								DAY 2	DAY 3	DAY 4					DAY 5		
			Pre Dose	SQ Injection	H O U R S															
					1	2	4	8	12	16	24	36	48	60	72	2	4	8	12	0
GENERAL																				
Informed Consent	X																			
Clinical Evaluation ^a	X																			
Physical Exam	X	w/WT																		
Vital signs ^b	X	X	X												Pre Dose					
12-lead EKG ^c	X	X3 ^g						X	X									X	X	
Concomitant Medication																				
Adverse Events Review																				
Confinement at Study Center																				
LABORATORY ASSESSMENTS AND DOSING																				
Hematology ^d	X	X																		
Serum Chemistry ^d	X	X																		
Urinalysis ^f	X	X																		
Urine Drug Screen ^f	X	X																		
HBV and HCV Serology	X																			
HIV 1/0/2 Test	X																			
Pregnancy Test ^e	X	X																		
AM0010 Dosing				SQ 1											SQ 2					SQ 3
PK Blood Draws			X												Pre Dose					Pre Dose
PD Blood Draws								X			X		X		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 semirecumbent position for at least 5 minutes.

^c EKG will be performed in subjects seated, semirecumbent, or supine for at least 5 minutes.

^d Safety lab tests are outlined in [Table 10.2.1](#).

^e Serum pregnancy testing in all females.

^f Urine lab tests are outlined in [Table 10.2.2](#).

^g X3 = Triplicate EKGs

Activities	DAY 6			DAY 7	DAY 8	DAY 9				DAY 10			DAY 11	DAY 12	DAY 15 EOS	
	H O U R S															
	0	4	8	0	0	0	2	4	8	12	24	36	48	60		72
GENERAL																
Physical Exam w/weight ^a																X
Vital signs ^b	Pre Dose					Pre Dose										X
12-lead EKG ^c									X	X						
Concomitant Medication																
Adverse Events Review																
Confinement at Study Center															D/C	
LABORATORY ASSESSMENTS AND DOSING																
Hematology ^d															X	X
Serum Chemistry ^d															X	X
Urinalysis ^f																X
Pregnancy Test ^e																X
AM0010 Dosing	SQ 4			SQ 5	SQ 6	SQ 7										
PK Blood Draws	Pre Dose				Pre Dose	Pre Dose	Pre Dose									
PD Blood Draws											X		X	X		X

^a 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 semirecumbent position for at least 5 minutes.

^c EKG will be performed in subjects seated, semirecumbent, or supine for at least 5 minutes.

^d Safety lab tests are outlined in [Table 10.2.1](#).

^e Serum pregnancy testing in all females.

^fUrine lab tests are outlined in [Table 10.2.2](#).

3.2 Study Endpoints

3.2.1 Primary Endpoints

The primary endpoints are PK parameters including maximum drug concentration ($C_{\max}$), time of maximum concentration observed ($T_{\max}$), area under the serum concentration over time curve (AUC), clearance (Cl), and half-life ($t_{1/2}$).

3.2.2 Secondary Endpoints

The secondary endpoints are incidence of adverse events (AE), injection site reactions, and clinically relevant changes in laboratory values, EKGs, and vital signs.

4 General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS[®] Version 9.3 or higher (SAS Institute, Cary, NC). All tables and data listings will appear in landscape format employing Courier New 9-point font.

Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. Frequency and percentage will be calculated for categorical variables.

No formal significance testing will be performed.

Unless stated otherwise, all summary tables will present descriptive statistics and/or frequencies by treatment, and all data listings will be sorted by subject number.

No algorithm for imputation of missing data will be employed.

If there are repeated measurements at a time point, the original measurement at that time point will be used in the summary tables. If the original measurement at that time point is missing, the next available measurement will be used in the summary tables.

Baseline will be defined as the last nonmissing assessment (including repeated and unscheduled assessments) before the first study drug administration on Day 1.

Unscheduled results will not be included in the summary tables except for determining Baseline, but will be presented in data listings.

4.1 Sample Size

This trial with AM0010 is expected to enroll 24 subjects (n=12 per cohort). At least 5 males and 5 females will be enrolled at each dose level. The sample size is based on practical considerations and is consistent for this type of study.

4.2 Randomization, Stratification, and Blinding

Randomization to 5 µg/kg or 10 µg/kg of AM0010 will be based on a randomization schedule prepared by PPD Biostatistics before the start of the study. The subjects will be randomized in a 1:1 ratio. Randomization will be stratified based on sex. At least 5 males and 5 females will be enrolled at each dose level.

After subjects have completed the screening procedures and are confirmed to be eligible for the study, they will be randomized to 1 of 2 dose levels.

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

Blinding is not applicable in this open-label study.

4.3 Analysis Populations

The following analysis populations will be used in this study:

- Safety Population—all subjects enrolled in the study who received at least one dose of study drug. This population will be used for safety analyses.
- All Randomized Population—all subjects enrolled in the study who get randomized. This population will be used for subject disposition summary and listings.
- PK Population - all subjects in the safety population who provide sufficient PK data to enable the accurate estimation of at least one serum PK parameter. 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.
- PD Population - all subjects in the safety population who provide sufficient PD data to enable the accurate estimation of at least one serum PD parameter. Subjects with protocol deviations, or who experience dosing or other issues which are deemed to affect the PD data, will be considered for exclusion from the PD Population on a case-by-case basis.

4.4 Changes in the Planned Analysis

Any changes to the analyses defined in the clinical study protocol or this statistical analysis plan will be documented in the clinical study report (CSR) for this study.

5 Subject Disposition

The number of subjects who complete the study and who do not complete the study, both overall and according to reasons for discontinuation from the study, will be summarized for the all randomized population, by treatment and overall.

The number of subjects in each analysis population will be summarized for the all randomized population.

Subject disposition and protocol deviations/violations will be presented in the data listings for the all randomized population. Subjects in the safety population with protocol deviations/violations will be presented in a summary table by deviation type and treatment.

6 Demographic and Baseline Characteristics

6.1 Demographics

Demographic information collected at screening will be listed for the all randomized population. Descriptive statistics will be calculated for the following continuous demographic characteristics: age (years), weight (kg), height (cm), and body mass index (kg/m^2). Frequency counts will be tabulated for the categorical variables of sex, race, and ethnicity. The summaries will be presented for the safety population.

6.2 Admission Criteria Deviations

Admission criteria deviations will be presented in a data listing.

6.3 Medical History

Medical history will be obtained at the screening visit.

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version to be delineated in the CSR). The medical history data will be presented in a data listing.

7 Treatments and Medications

7.1 Prior and Concomitant Medications

Prior and concomitant medications taken within 28 days before study Day 1 and throughout the study will be recorded on the electronic case report form (eCRF). All prior and concomitant medications will be coded according to the World Health Organization-Drug Dictionary, (WHODrug; version to be delineated in the CSR) and presented in a data listing.

7.2 Medical or Surgical Treatment Procedures

Medical or surgical treatment procedures will be presented in a data listing.

7.3 Study Treatments

Study drug administration will be presented in a data listing.

8 Population PK (PopPK) and Pharmacokinetic Modelling Assessments

If required, the PopPK and PK modelling analysis will be specified in a separate analysis plan.

9 Safety Analysis

9.1 Adverse Events

An AE is any untoward medical occurrence in a patient or subject under clinical investigation due to a pharmaceutical (investigational) product that does not necessarily have a causal relationship with AM0010. 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 serious adverse event (SAE) is any adverse event occurring at any dose 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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

Treatment-emergent adverse events (TEAEs) are defined as events with onset on or after initiation of study medication.

Adverse events will be coded using MedDRA (version to be delineated in the CSR).

All AEs will be presented in a listing. All TEAEs will be summarized for the safety population by treatment and overall.

All AE summary tables will be sorted by system organ class (SOC) and preferred term (PT), and will be based on TEAEs. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term 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 incident or most related incident. Percentages will be based on the number of subjects within each treatment and overall.

The relationship to study drug of all AEs will be evaluated by the investigator as not related or related. TEAEs will be summarized by treatment, overall, and relationship. Treatment-related TEAEs will be summarized by treatment and overall.

The severity of all AEs will be graded using Grade 1 through Grade 5 as defined in the Common Terminology Criteria for Adverse Events v 4.03 (CTCAE: National Cancer Institute) definitions. A summary of TEAEs will be presented by treatment and overall, and severity.

All TEAEs resulting in early discontinuation will be presented in a data listing.

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

9.2 Clinical Laboratory Evaluations

The following laboratory tests will be performed:

Table 10.2.1 Blood Samples Collected During the Course of the Study

Serum Chemistry	Hematology	Virology	Other
Sodium Potassium Chloride Bicarbonate Glucose BUN/Urea Creatinine ^a LDH ALT AST GGT Alkaline phosphatase Total bilirubin Amylase Total protein Albumin Calcium Magnesium Phosphate	RBC WBC Hemoglobin Hematocrit Reticulocyte counts Platelet Count Differential Neutrophils Lymphocytes Monocytes	Anti-HCV Antibody Hepatitis B Surface Antigen HIV 1/0/2 Testing	FSH

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; RBC = red blood cell; WBC = white blood cell

^a Estimated creatinine clearance (CLcr)/glomerular filtration rate will be calculated based on the Cockcroft-Gault formula using actual body weight: $CLcr (mL/min) = (140 - \text{age [years]}) * \text{weight (kg)} / (\text{serum creatinine [mg/dL]} * 72)$. If the subject is female, multiply the quantity by 0.85. Performed at screening only

Table 10.2.2 Urine Samples Collected During the Course of the Study

Urinalysis		Urine Drug Screen
Specific gravity	WBC	Amphetamine
pH	RBC	Cocaine
Blood	Epithelial Cells	Opiates
Protein	Bacteria	Benzodiazepines
Glucose	Casts	Barbiturates
Ketones	Crystals	Methadone
Bilirubin	Urobilinogen	Alcohol/Ethanol
		Cannabinoids

Clinical laboratory tests for serum chemistry, hematology will be performed at Screening, on Day 0, Day 12, and on Day 15/EOS or at Early Termination (ET) if applicable. Urinalysis and serum pregnancy tests will be collected at Screening, on Day 0 and on Day 15/EOS or at ET if applicable. Tests for urine drug screen and will be performed at Screening and on Day 0. Virology tests will be performed at Screening only.

Results from clinical laboratory tests will be presented in the data listings. Values outside of normal range will be flagged. Actual results and change from baseline for hematology, serum chemistry and urinalysis will be summarized by visit and treatment. Refer to [Section 4](#) for the definition of baseline.

9.3 Vital Signs

Vital sign measurements (systolic and diastolic blood pressures, heart rate (HR), respiratory rate, and temperature) will be collected at Screening, on Day 0, at predose on Day 1, Day 4, Day 6 and Day 9, and on Day 15/EOS or at ET if applicable. Subjects must be seated or in a semirecumbent position for at least 5 minutes prior to vital signs measurement.

All vital sign measurements will be presented in a data listing. The actual values and change from baseline values will be summarized by visit, time point, and treatment. Refer to [Section 4](#) for the definition of baseline.

Any abnormal measurements may be repeated and reported as adverse events, if appropriate.

9.4 12-Lead Electrocardiograms

Electrocardiogram assessments include HR, PR interval, QRS interval, QT interval, and QT interval corrected for HR using Fridericia's formula (QTcF). Baseline EKGs will be performed in triplicate on Day 0. Single EKGs will be performed at Screening, at predose, 8 hours and 12 hours postdose on Day 1, Day 4, and Day 9, at predose only on Day 6, and on Day 15/EOS or at ET if applicable. Subjects will be seated, semirecumbent, or supine for at least 5 minutes before the EKG is obtained.

All EKG findings will be presented in a data listing. The actual values and change from baseline values will be summarized by visit, time point, and treatment. Refer to [Section 4](#) for the definition of baseline.

9.5 Physical Examination

Physical examinations will be performed at Screening, on Day 0, and on Day 15/EOS or at ET if applicable.

Height will be obtained at Screening only. Weight will be performed at Screening, on Day 0, and on Day 15/EOS or at ET if applicable.

Predose abnormal findings will be reported as medical history. Any clinically significant changes from Day 0 physical examination will be reported as AEs.

All physical examination results will be presented in a data listing.

10. Pharmacokinetics

10.1. Pharmacokinetic Concentration Data

10.2. Serum Pharmacokinetic Concentrations

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

- Day 1: predose, 1, 2, 4, 8, 12, 16, 24, 36, 48, 60 and 72 hours (Day 4 predose) after SQ dosing
- Day 4: predose, 2, 4, 8, 12 and 24 hours (Day 5 predose) after SQ dosing
- Day 6: predose, 4, 8 and 24 hours (Day 7 predose) after SQ dosing
- Day 8: predose
- Day 9: predose, 2, 4, 8, 12, 24, 36, 48, 60 and 72 hours after SQ dosing

Individual serum concentrations of AM0010 will be listed using the Safety Population. Individual serum concentration versus actual time profiles will be plotted for each subject using the Safety Population.

The following descriptive statistics will be provided for each dose level, and each sampling time used for the PK analysis (Day 1 and Day 9 zero to 72 hours postdose) using the PK Population: number of observations (n), arithmetic mean, arithmetic SD, arithmetic coefficient of variation (CV), median, minimum and maximum. Mean serum concentration versus nominal time profiles will be plotted, where possible, using the PK Population.

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

10.3. Pharmacokinetic Parameters

10.3.1. 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 may be set to zero.

10.3.2. 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} 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.

10.4. 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):

Ctrough	Trough (predose) serum concentration [Days 5, 6, 7, 8 and 9]
On Day 1	
C _{max}	Maximum serum concentration
t _{max}	Time of the maximum serum concentration
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
AUC ₀₋₂₄	Area under the concentration versus time curve from time 0 to nominal 24 hours post-dose
AUC _{0-inf}	Area under the concentration versus time curve from time 0 extrapolated to infinity
t _{1/2}	Apparent terminal elimination half-life, calculated as $[(\ln 2)/\lambda_z]$. If the length of the time interval used to determine λ_z 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 λ_z will be flagged).
CL/F	Total body clearance, calculated as: Dose / AUC _{0-inf}
V _z /F	Volume of distribution
On Day 9	
C _{maxss}	Maximum serum concentration
t _{maxss}	Time of the maximum serum concentration
AUC _{0-tss}	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

AUC0-tau	Area under the concentration versus time curve within a dosing interval (i.e. 24 hours)
t _{1/2} ss	Apparent terminal elimination half-life, calculated as $[(\ln 2)/\lambda_z]$. 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 _{ss} /F	Total body clearance, calculated as: Dose / AUC0-tau
RAC _{max}	Accumulation ratio for C _{max} , calculated as C _{max} on Day 9/ C _{max} on Day 1
RAAUC	Accumulation ratio for AUC, calculated as AUC0-tau on Day 9/ AUC0-24 on Day 1

In addition to the above pharmacokinetic variables, which will be listed and summarized on Days 1 and 9, 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	Adjusted r ² , the coefficient of determination (goodness of fit statistic); Kel will only be retained if adjusted r ² ≥ 0.80.
%AUCext	Percentage of AUC extrapolated the last quantifiable concentration to infinity, AUC0-inf will be listed but excluded from summary statistics when %AUCext is greater than 30%.

Actual doses and 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 dose level using the PK Population. The following descriptive statistics will be provided for all PK parameters, with the exception of t_{max}, at each dose level using the PK Population: number of observations (n), geometric mean, geometric mean coefficient of variation (geometric CV), arithmetic mean, arithmetic SD, arithmetic coefficient of variation (CV), median, minimum and maximum. The parameter t_{max} and t_{max}ss will only summarize n, median, minimum and maximum.

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 t_{max} and t_{max}ss, 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 mean, geometric CV, Mean, SD, CV, median, minimum, and maximum should be presented to the same precision as the listings.

10.5. Pharmacokinetic Statistical Analyses

No formal statistical analysis is required for this study

11. Pharmacodynamics

11.1. Biomarker Concentrations

Immune related cytokines in the serum will be collected at the following time points:

- Day 1: predose, 4, 12, 24 and 48 hours after SQ dosing
- Day 4: predose
- Day 5: predose
- Day 6: predose
- Day 7: predose
- Day 8: predose
- Day 9: predose, 4, 12, 24, 48 and 72 hours after SQ dosing

Individual serum immune related cytokines (absolute and baseline-adjusted) will be listed using the Safety Population. Baseline will be defined as the predose value on Days 1 and 9. Individual serum concentration versus time profiles will be plotted for each subject using the Safety Population on Days 1 and 9. If the predose sample is missing on Day 1 or Day 9 no baseline adjusted concentrations will be calculated for the day.

The following descriptive statistics will be provided for each dose level and sampling time used for the PD analysis (Day 1 and 9 zero to 72 hours postdose) using the PD Population: n, arithmetic mean, SD, CV, median, minimum and maximum. Mean serum concentration (absolute and baseline-adjusted) versus time profiles will be plotted on Days 1 and 9, where possible, using the PD Population.

11.2. Pharmacodynamic Parameters

The following serum PD parameters will be estimated for serum immune related cytokines (on Days 1 and 9) via non-compartment analysis using Phoenix WinNonlin version 6.4 or higher (version to be delineated in the CSR):

Emax	Maximum effect
TEmax	Time of the maximum effect
AUEC0-24	Area under the effect versus time curve from time 0 to nominal 24 hours postdose

Absolute and baseline-adjusted values will be used to estimate PD parameters for serum immune related cytokines on Days 1 and 9. Baseline will be defined as the predose value on

each study day, and negative baseline-adjusted values will be included in the analysis. If the predose sample is missing on Day 1 or Day 9 no baseline adjusted concentrations will be calculated for the day.

Individual PD parameters of serum immune related cytokines (absolute and baseline-adjusted) will be listed using the Safety Population and summarised using the PD Population. Where data are available for more than one subject at a given dose level, the following descriptive statistics will be provided for all PD parameters, with the exception of TEmax, at each dose level using the PD Population: n, arithmetic mean, SD, CV, median, minimum and maximum. The parameter TEmax will only summarize n, median, minimum and maximum.

For the listings, concentration data will be presented to the same precision as the data is received and all baseline-adjusted concentrations will be presented to 3 significant figures. All PD parameters will be presented in the listings to 3 significant figures with the exception of TEmax, 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.
- Mean, SD, median, minimum, and maximum should be presented to the same precision as the listings.

11.3. Pharmacodynamic Statistical Analyses

No formal statistical analysis is required for this study.

12. Interim Analysis

No interim PK or PD analysis is anticipated for this study

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ARMO Biosciences, Inc

AM0010-801

**A Phase 1 Study to Evaluate the Pharmacokinetics of Single and Multiple
Doses of AM0010 in Healthy Adult Subjects**

29 MAR 2019

Statistical Analysis Plan Amendment

Version 1.0

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Listing of Abbreviations

Abbreviation	Definition
%AUCext	percentage of AUC extrapolated the last quantifiable concentration to infinity
AE	adverse event
AM0010	PEGylated recombinant human interleukin 10
AUC0-24	area under the concentration versus time curve from time 0 to nominal 24 hours post-dose
AUC0-inf	area under the concentration versus time curve from time 0 extrapolated to infinity
AUC0-t	area under the concentration versus time curve from time 0 to the last observed time point
AUC0-tau	area under the concentration versus time curve within a dosing interval (i.e. 24 hours)
AUEC0-24	area under the effect versus time curve from time 0 to nominal 24 hours postdose
BLQ	below the limit of quantification
CL/F	total body clearance
Cmax	maximum serum concentration
Ctrough	trough (predose) serum concentration
CSR	clinical study report
CV	coefficient of variation
eCRF	electronic case report form
EKG	electrocardiogram
Emax	maximum effect
EOS	end of study
ET	early termination
HR	heart rate
Kel	terminal elimination rate constant
MedDRA	medical dictionary for regulatory activities
n	number of subjects
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PopPK	population PK
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAAUC	accumulation ratio for AUC
RACmax	accumulation ratio for Cmax
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SQ	subcutaneous
t _{1/2}	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TEmax	time of maximum effect

Abbreviation	Definition
tmax	time of the maximum serum concentration
Vz/F	volume of distribution
WHODrug	World Health Organization Drug Dictionary

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.

In the current study AM0010-801, the pharmacokinetics (PK) of AM0010 at two dose levels (5 µg/kg and 10 µg/kg) will be evaluated. Based on an interim PK analysis from the First-in-Human study AM0010-001, apparent clearance varied as a function of dose. In this clinical study, doses up to 40 µg/kg were safe and well-tolerated. In addition, dose levels between 5 µg/kg and 20 µg/kg have been associated with clinical activity in patients with advanced solid malignancies. Because these dose levels will be used in the Phase 3 program, detailed evaluation of the PK of AM0010 at 5 µg/kg and 10 µg/kg are warranted.

2 Objectives

2.1 Primary Objectives

The primary objective is to characterize the PK of AM0010 after single and multiple subcutaneous (SQ) injections in healthy adult subjects.

2.2 Secondary Objective

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

3 Investigational Plan

3.1 Overall Study Design and Plan

The study is an open-label, single followed by multiple dose study to evaluate the PK/ pharmacodynamic (PD) of AM0010 in healthy adult subjects. Subjects will receive a single SQ injection of AM0010 and be followed for 72 hours with PK (serum) sampling at multiple time points. Subjects will then receive AM0010 at the assigned dose SQ once daily × 6 and have PK samples collected at multiple time points between injections as well as after the final injection of AM0010. Two dose levels (5 µg/kg and 10 µg/kg) will be evaluated with 12 subjects enrolled at each dose level.

Twenty-four subjects will be randomly assigned in a 1:1 ratio to 2 dose levels of AM0010 (5 µg/kg and 10 µg/kg). AM0010 at 5 µg/kg will be administered as one of 2 fixed doses (i.e., either 400 µg in 200 µL for body weights ≤ 80 kg or 800 µg in 400 µL for body weight > 80 kg) based on the subject's weight during the course of the study. AM0010 at 10 µg/kg will be administered as one of two fixed doses (i.e., either 800 µg in 400 µL for body weights ≤ 80

kg or 1600 µg in 800 µL for body weight > 80 kg) based on the subject's weight during the course of the study.

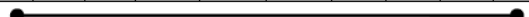
Table 3.1.1 AM0010 Dosing

ARM	Dose Level	Concentration	Subject Weight	Dose and Volume AM0010
1	5 µg/kg	2 mg/mL	≤80 kg	400 µg in 0.2 mL
			>80 kg	800 µg in 0.4 mL
2	10 µg/kg	2 mg/mL	≤80 kg	800 µg in 0.4 mL
			>80 kg	1600 µg in 0.8 mL

Subjects will be admitted to an inpatient research facility on Day 0 and remain in residence from Day 0 to Day 12. On Day 0, baseline procedures including physical examination, safety laboratory tests, vital signs, electrocardiogram (EKG), and serum pregnancy (in all females) will be performed. Prior to dosing on the morning of Day 1, a sample for PK/PD will be drawn prior to dosing, and subjects will then receive a SQ injection of AM0010. On the morning of Days 4 through 9, subjects will receive a SQ injection of AM0010 at the same dose that was administered on Day 1.

The subjects will be discharged from the inpatient research facility on the morning of Day 12 after completion of study-related procedures. The Day 15 End-of-Study (EOS) visit to the research site will be on an outpatient basis for, safety assessments, and safety blood draw time points outlined in the Schedule of Events [Table 3.1.2](#).

Table 3.1.2 Schedule of Study Events

Activities	Screening -28 Days	Baseline Day 0	DAY 1								DAY 2	DAY 3	DAY 4					DAY 5		
			Pre Dose	SQ Injection	H O U R S															
					1	2	4	8	12	16	24	36	48	60	72	2	4	8	12	0
GENERAL																				
Informed Consent	X																			
Clinical Evaluation ^a	X																			
Physical Exam	X	w/WT																		
Vital signs ^b	X	X	X												Pre Dose					
12-lead EKG ^c	X	X3 ^g						X	X									X	X	
Concomitant Medication																				
Adverse Events Review																				
Confinement at Study Center																				
LABORATORY ASSESSMENTS AND DOSING																				
Hematology ^d	X	X																		
Serum Chemistry ^d	X	X																		
Urinalysis ^f	X	X																		
Urine Drug Screen ^f	X	X																		
HBV and HCV Serology	X																			
HIV 1/0/2 Test	X																			
Pregnancy Test ^e	X	X																		
AM0010 Dosing				SQ 1											SQ 2					SQ 3
PK Blood Draws			X												Pre Dose					Pre Dose
PD Blood Draws							X		X		X		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 semirecumbent position for at least 5 minutes.

^c EKG will be performed in subjects seated, semirecumbent, or supine for at least 5 minutes.

^d Safety lab tests are outlined in [Table 9.2.1](#).

^e Serum pregnancy testing in all females.

^f Urine lab tests are outlined in [Table 9.2.2](#).

^g X3 = Triplicate EKGs

^a 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 semirecumbent position for at least 5 minutes.

^c EKG will be performed in subjects seated, semirecumbent, or supine for at least 5 minutes.

^d Safety lab tests are outlined in [Table 9.2.1](#).

^e Serum pregnancy testing in all females.

^f Urine lab tests are outlined in [Table 9.2.2](#).

3.2 Study Endpoints

3.2.1 Primary Endpoints

The primary PK endpoints are maximum drug concentration ($C_{\max}$), time of maximum concentration observed ($T_{\max}$), area under the serum concentration over time curve (AUC), clearance (Cl), and half-life ($t_{1/2}$).

The primary PD endpoints are minimum effect ($E_{\min}$), time of maximum effect ($TE_{\max}$), maximum effect ($E_{\max}$), time of minimum effect ($TE_{\min}$) and area under the effect versus time curve (AUEC).

3.2.2 Secondary Endpoints

The secondary endpoints are incidence of adverse events (AE), injection site reactions, and clinically relevant changes in laboratory values, EKGs, and vital signs.

4 General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS[®] Version 9.3 or higher (SAS Institute, Cary, NC). All tables and data listings will appear in landscape format employing Courier New 9-point font.

Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. Frequency and percentage will be calculated for categorical variables.

No formal significance testing will be performed.

Unless stated otherwise, all summary tables will present descriptive statistics and/or frequencies by treatment, and all data listings will be sorted by subject number.

No algorithm for imputation of missing data will be employed.

If there are repeated measurements at a time point, the original measurement at that time point will be used in the summary tables. If the original measurement at that time point is missing, the next available measurement will be used in the summary tables.

Baseline will be defined as the last nonmissing assessment (including repeated and unscheduled assessments) before the first study drug administration on Day 1.

Unscheduled results will not be included in the summary tables except for determining Baseline, but will be presented in data listings.

4.1 Sample Size

This trial with AM0010 is expected to enroll 24 subjects (n=12 per cohort). At least 5 males and 5 females will be enrolled at each dose level. The sample size is based on practical considerations and is consistent for this type of study.

4.2 Randomization, Stratification, and Blinding

Randomization to 5 µg/kg or 10 µg/kg of AM0010 will be based on a randomization schedule prepared by PPD Biostatistics before the start of the study. The subjects will be randomized in a 1:1 ratio. Randomization will be stratified based on sex. At least 5 males and 5 females will be enrolled at each dose level.

After subjects have completed the screening procedures and are confirmed to be eligible for the study, they will be randomized to 1 of 2 dose levels.

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

Blinding is not applicable in this open-label study.

4.3 Analysis Populations

The following analysis populations will be used in this study:

- Safety Population—all subjects enrolled in the study who received at least one dose of study drug. This population will be used for safety analyses.
- All Randomized Population—all subjects enrolled in the study who get randomized. This population will be used for subject disposition summary and listings.
- PK Population - all subjects in the safety population who provide sufficient PK data to enable the accurate estimation 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.
- PD Population - all subjects in the safety population who provide sufficient PD data to enable the accurate estimation of at least TE_{max} and E_{max} . Subjects with protocol deviations, or who experience dosing or other issues which are deemed to affect the PD data, will be considered for exclusion from the PD Population on a case-by-case basis.
- The PK/PD population - all subjects in the safety population who provide sufficient PK data to enable the accurate estimation of at least C_{max} and T_{max} and sufficient PD data to enable the accurate estimation of at least TE_{max} and E_{max} . Subjects with protocol deviations, or who experience dosing or other issues which are deemed to

affect the PK/PD data, will be considered for exclusion from the PK Population on a case-by-case basis.

4.4 Changes in the Planned Analysis

Any changes to the analyses defined in the clinical study protocol or this statistical analysis plan will be documented in the clinical study report (CSR) for this study.

5 Subject Disposition

The number of subjects who complete the study and who do not complete the study, both overall and according to reasons for discontinuation from the study, will be summarized for the all randomized population, by treatment and overall.

The number of subjects in each analysis population will be summarized for the all randomized population.

Subject disposition and protocol deviations/violations will be presented in the data listings for the all randomized population. Subjects in the safety population with protocol deviations/violations will be presented in a summary table by deviation type and treatment.

6 Demographic and Baseline Characteristics

6.1 Demographics

Demographic information collected at screening will be listed for the all randomized population. Descriptive statistics will be calculated for the following continuous demographic characteristics: age (years), weight (kg), height (cm), and body mass index (kg/m^2). Frequency counts will be tabulated for the categorical variables of sex, race, and ethnicity. The summaries will be presented for the safety population.

6.2 Admission Criteria Deviations

Admission criteria deviations will be presented in a data listing.

6.3 Medical History

Medical history will be obtained at the screening visit.

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version to be delineated in the CSR). The medical history data will be presented in a data listing.

7 Treatments and Medications

7.1 Prior and Concomitant Medications

Prior and concomitant medications taken within 28 days before study Day 1 and throughout the study will be recorded on the electronic case report form (eCRF). All prior and concomitant medications will be coded according to the World Health Organization-Drug Dictionary, (WHODrug; version to be delineated in the CSR) and presented in a data listing.

7.2 Medical or Surgical Treatment Procedures

Medical or surgical treatment procedures will be presented in a data listing.

7.3 Study Treatments

Study drug administration will be presented in a data listing.

8 Population PK (PopPK) and Pharmacokinetic Modelling Assessments

If required, the PopPK and PK modelling analysis will be specified in a separate analysis plan.

9 Safety Analysis

9.1 Adverse Events

An AE is any untoward medical occurrence in a patient or subject under clinical investigation due to a pharmaceutical (investigational) product that does not necessarily have a causal relationship with AM0010. 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 serious adverse event (SAE) is any adverse event occurring at any dose 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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment,

they may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

Treatment-emergent adverse events (TEAEs) are defined as events with onset on or after initiation of study medication.

Adverse events will be coded using MedDRA (version to be delineated in the CSR).

All AEs will be presented in a listing. All TEAEs will be summarized for the safety population by treatment and overall.

All AE summary tables will be sorted by system organ class (SOC) and preferred term (PT), and will be based on TEAEs. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term 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 incident or most related incident. Percentages will be based on the number of subjects within each treatment and overall.

The relationship to study drug of all AEs will be evaluated by the investigator as not related or related. TEAEs will be summarized by treatment, overall, and relationship. Treatment-related TEAEs will be summarized by treatment and overall.

The severity of all AEs will be graded using Grade 1 through Grade 5 as defined in the Common Terminology Criteria for Adverse Events v 4.03 (CTCAE: National Cancer Institute) definitions. A summary of TEAEs will be presented by treatment and overall, and severity.

All TEAEs resulting in early discontinuation will be presented in a data listing.

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

9.2 Clinical Laboratory Evaluations

The following laboratory tests will be performed:

Table 9.2.1 Blood Samples Collected During the Course of the Study

Serum Chemistry	Hematology	Virology	Other
Sodium Potassium Chloride Bicarbonate Glucose BUN/Urea Creatinine ^a LDH ALT AST GGT Alkaline phosphatase Total bilirubin Amylase Total protein Albumin Calcium Magnesium Phosphate	RBC WBC Hemoglobin Hematocrit Reticulocyte counts Platelet Count Differential Neutrophils Lymphocytes Monocytes	Anti-HCV Antibody Hepatitis B Surface Antigen HIV 1/0/2 Testing	FSH

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; RBC = red blood cell; WBC = white blood cell

^a Estimated creatinine clearance (CLcr)/glomerular filtration rate will be calculated based on the Cockcroft-Gault formula using actual body weight: CLcr (mL/min) = (140 – age [years])* weight (kg) / (serum creatinine [mg/dL]*72). If the subject is female, multiply the quantity by 0.85. Performed at screening only

Table 9.2.2 Urine Samples Collected During the Course of the Study

Urinalysis	Urine Drug Screen
Specific gravity pH Blood Protein Glucose Ketones Bilirubin	WBC RBC Epithelial Cells Bacteria Casts Crystals Urobilinogen
	Amphetamine Cocaine Opiates Benzodiazepines Barbiturates Methadone Alcohol/Ethanol Cannabinoids

Clinical laboratory tests for serum chemistry, hematology will be performed at Screening, on Day 0, Day 12, and on Day 15/EOS or at Early Termination (ET) if applicable. Urinalysis and serum pregnancy tests will be collected at Screening, on Day 0 and on Day 15/EOS or at ET if applicable. Tests for urine drug screen and will be performed at Screening and on Day 0. Virology tests will be performed at Screening only.

Results from clinical laboratory tests will be presented in the data listings. Values outside of normal range will be flagged. Actual results and change from baseline for hematology, serum

chemistry and urinalysis will be summarized by visit and treatment. Refer to [Section 4](#) for the definition of baseline.

9.3 Vital Signs

Vital sign measurements (systolic and diastolic blood pressures, heart rate (HR), respiratory rate, and temperature) will be collected at Screening, on Day 0, at predose on Day 1, Day 4, Day 6 and Day 9, and on Day 15/EOS or at ET if applicable. Subjects must be seated or in a semirecumbent position for at least 5 minutes prior to vital signs measurement.

All vital sign measurements will be presented in a data listing. The actual values and change from baseline values will be summarized by visit, time point, and treatment. Refer to [Section 4](#) for the definition of baseline.

Any abnormal measurements may be repeated and reported as adverse events, if appropriate.

9.4 12-Lead Electrocardiograms

Electrocardiogram assessments include HR, PR interval, QRS interval, QT interval, and QT interval corrected for HR using Fridericia's formula (QTcF). Baseline EKGs will be performed in triplicate on Day 0. Single EKGs will be performed at Screening, at predose, 8 hours and 12 hours postdose on Day 1, Day 4, and Day 9, at predose only on Day 6, and on Day 15/EOS or at ET if applicable. Subjects will be seated, semirecumbent, or supine for at least 5 minutes before the EKG is obtained.

All EKG findings will be presented in a data listing. The actual values and change from baseline values will be summarized by visit, time point, and treatment. Refer to [Section 4](#) for the definition of baseline.

9.5 Physical Examination

Physical examinations will be performed at Screening, on Day 0, and on Day 15/EOS or at ET if applicable.

Height will be obtained at Screening only. Weight will be performed at Screening, on Day 0, and on Day 15/EOS or at ET if applicable.

Predose abnormal findings will be reported as medical history. Any clinically significant changes from Day 0 physical examination will be reported as AEs.

All physical examination results will be presented in a data listing.

10. Pharmacokinetics

10.1. Pharmacokinetic Concentration Data

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

- Day 1: predose, 1, 2, 4, 8, 12, 16, 24, 36, 48, 60 and 72 hours (Day 4 predose) after SQ dosing
- Day 4: predose, 2, 4, 8, 12 and 24 hours (Day 5 predose) after SQ dosing
- Day 6: predose, 4, 8 and 24 hours (Day 7 predose) after SQ dosing
- Day 8: predose
- Day 9: predose, 2, 4, 8, 12, 24, 36, 48, 60 and 72 hours after SQ dosing

Individual serum concentrations, dose normalised serum concentrations, actual sampling times and time deviations of AM0010 will be listed to the same precision as the raw data using the Safety Population. Individual serum concentration and dose normalised 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 and dose normalised AM0010 serum concentrations for each dose level, and each sampling time used for the PK analysis (Day 1 and Day 9 zero to 72 hours postdose) using the PK Population: number of observations (n), arithmetic mean, arithmetic SD, arithmetic coefficient of variation (CV), median, minimum and maximum.

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

10.2. 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 may be set to zero.

10.3. 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} for a subject, all values and PK parameters will be listed, flagged and included in the primary 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 profile 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 5% on the Day 1 PK parameters.

10.4. 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):

Ctrough	Trough (predose) serum concentration [Days 5, 6, 7, 8 and 9]
On Day 1	
C _{max}	Maximum serum concentration
t _{max}	Time of the maximum serum concentration
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
AUC ₀₋₂₄	Area under the concentration versus time curve from time 0 to nominal 24 hours post-dose
AUC _{0-inf}	Area under the concentration versus time curve from time 0 extrapolated to infinity
t _{1/2}	Apparent terminal elimination half-life, calculated as $[(\ln 2)/\lambda_z]$. If the length of the time interval used to determine λ_z 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 λ_z will be flagged).
CL/F	Total body clearance, calculated as: Dose / AUC0-inf
Vz/F	Volume of distribution
On Day 9	
Cmin	Minimum observed serum concentration
Cmaxss	Maximum observed serum concentration at steady state
tmaxss	Time of the maximum observed serum concentration at steady state
AUC0-tss	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
AUC0-tau	Area under the concentration versus time curve within a dosing interval (i.e. 24 hours)
t1/2ss	Apparent terminal elimination half-life, calculated as $[(\ln 2)/\lambda_z]$. 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).
CLss/F	Total body clearance, calculated as: Dose / AUC0-tau
RACmax	Accumulation ratio for Cmax, calculated as Cmax on Day 9/ Cmax on Day 1
RAAUC	Accumulation ratio for AUC, calculated as AUC0-tau on Day 9/ AUC0-24 on Day 1

In addition to the above pharmacokinetic variables, which will be listed and summarized on Days 1 and 9, 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	Adjusted r^2 , the coefficient of determination (goodness of fit statistic); Kel will only be retained if adjusted $r^2 \geq 0.80$.
%AUCext	Percentage of AUC extrapolated 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 doses and 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 dose level using the PK Population. The following descriptive statistics will be provided for all PK parameters, with the exception of tmax and t1/2, at each dose level using the PK Population: number of observations (n), geometric mean, geometric mean coefficient of variation (geometric CV), arithmetic mean, arithmetic SD, arithmetic coefficient of variation (CV), median, minimum and maximum. The parameter tmax and tmaxss will only summarize n, median, minimum and maximum, t1/2 will only summarize geometric mean and CV; n, minimum, maximum, and median.

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 and tmaxss, 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 as a whole interger.
Geometric mean, Mean, SD, median, minimum, and maximum should be presented to the same precision as the listings.

10.5. Pharmacokinetic Statistical Analyses

A non-linear power model will be used to assess dose-proportionality for AM0010 on Days 1 and 9 separately. The proportional relationship between the expected value of each parameter [E(y)] and dose is written as a power function:

$$E(y) = a * dose^b \text{ [Equation 1]}$$

where 'a' is a constant, 'b' is the proportionality constant and 'y' is the parameter of interest (AUC0-tau/AUC0-24, Cmax and Cmin). The exponent, b, will be estimated by performing a linear regression of ln(parameter) on ln(dose). The exponent, b, is the estimated slope of the resulting regression line, since taking logs of Equation 1 gives the linear relationship:

$$\ln(y) = \ln(a) + b * \ln(dose) \text{ [Equation 2]}$$

The relationship is dose proportional when b = 1.

To test for lack of fit of the power model, a quadratic term [ln(dose)²] will be included in a separate model to test for a systematic departure from linearity; a p-value < 0.05 would indicate significant lack of fit of the power model.

The accumulation ratio will be estimated by making comparisons of AUC0-tau and Cmax on Day 9 with corresponding estimates on Day 1 for each treatment separately; a mixed-effects model will be fitted to log-transformed AUC0-tau and Cmax including day (Day 1 or 9) as a fixed effect and subject as a random effect. This model will be used to estimate the

accumulation ratio (Day 9 / Day 1) with 95% CIs for each treatment. The geometric least squares means and ratio with 95% CIs will be tabulated by treatment and parameter.

Values of time of maximum serum drug concentration (Tmax) will be analysed nonparametrically using the Wilcoxon signed rank test. The median of differences and 90% CIs for the medians of differences of Tmax will be calculated to assess the effect of dose and day.

11. Pharmacodynamics

11.1. Biomarker Concentrations

Immune related cytokines in the serum will be collected at the following time points:

- Day 1: predose, 4, 12, 24 and 48 hours after SQ dosing
- Day 4: predose (72 hours)
- Day 5: predose (96 hours)
- Day 6: predose (120 hours)
- Day 7: predose (144 hours)
- Day 8: predose (168 hours)
- Day 9: predose (192 hours), 4 (196 hours), 12 (204 hours), 24 (216 hours), 48 (240 hours) and 72 (264 hours) hours after SQ dosing

Values in parentheses represent the times relative to the first dose

Individual serum immune related cytokines (absolute and baseline-adjusted) will be listed using the Safety Population. Baseline will be defined as the predose value on Days 1 and 9. Individual serum concentration versus time profiles will be plotted for each subject using the Safety Population on Days 1 and 9. If the predose sample is missing on Day 1 or Day 9 no baseline adjusted concentrations will be calculated for the day.

Samples collected outside the allowable window ($\pm 10\%$ of the protocol time) will be flagged and excluded from the calculation of summary statistics. The following descriptive statistics will be provided for each dose level and sampling time used for the PD analysis (Day to Day 12) using the PD Population: n, arithmetic mean, SD, CV, median, minimum and maximum. Mean serum concentration (absolute and baseline-adjusted) versus time profiles will be plotted across all days, where possible, using the PD Population.

11.2. Pharmacodynamic Parameters

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

Emin	Minimum effect
TEmin	Time of the minimum effect
Emax	Maximum effect

TE _{max}	Time of the maximum effect
AUE _{Clast}	Area under the effect 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

Absolute and baseline-adjusted values will be used to estimate PD parameters for serum immune related cytokines. Baseline will be defined as the predose value on Day 1, and negative baseline-adjusted values will be included in the analysis. If the predose sample is missing on Day 1 no baseline adjusted concentrations will be calculated for the day.

Individual PD parameters of serum immune related cytokines (absolute and baseline-adjusted) will be listed using the Safety Population and summarised using the PD Population. Where data are available for more than one subject at a given dose level, the following descriptive statistics will be provided for all PD parameters, with the exception of TE_{max} and TE_{min}, at each dose level using the PD Population: n, arithmetic mean, SD, CV, median, minimum and maximum. The parameter TE_{max} and TE_{min} will only summarize n, median, minimum and maximum.

For the listings, concentration data will be presented to the same precision as the data is received and all baseline-adjusted concentrations will be presented to 3 significant figures. All PD parameters will be presented in the listings to 3 significant figures with the exception of TE_{max} and TE_{min}, 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.
- CV should be presented as an integer.
- Mean, SD, median, minimum, and maximum should be presented to the same precision as the listings.

11.3. Pharmacodynamic Statistical Analyses

A non-linear power model will be used to assess dose-proportionality for serum immune related cytokines. The proportional relationship between the expected value of each parameter [E(y)] and dose is written as a power function:

$$E(y) = a * dose^b \text{ [Equation 1]}$$

where 'a' is a constant, 'b' is the proportionality constant and 'y' is the parameter of interest (E_{min}, E_{max} and AUE_{Clast}). The exponent, b, will be estimated by performing a linear regression of ln(parameter) on ln(dose). The exponent, b, is the estimated slope of the resulting regression line, since taking logs of Equation 1 gives the linear relationship:

$$\ln(y) = \ln(a) + b * \ln(dose) \text{ [Equation 2]}$$

The relationship is dose proportional when $b = 1$.

To test for lack of fit of the power model, a quadratic term $[\ln(\text{dose})^2]$ will be included in a separate model to test for a systematic departure from linearity; a p-value < 0.05 would indicate significant lack of fit of the power model.

Values of time of maximum and minimum effect (TE_{max} and TE_{min}) will be analysed nonparametrically using the Wilcoxon signed rank test. The median of differences and 90% CIs for the medians of differences of T_{max} will be calculated to assess the effect of dose and day.

12. PK/PD Analysis

The PK/PD relationship between AM0010 and serum immune related cytokines will be assessed. Scatter plots of individual serum concentrations of AM0010 will be presented versus individual serum immune related cytokines over time as well as with time-matched PK and cytokine samples.

In addition, the relationship between individual time-matched concentrations of AM0010 and individual serum immune related cytokines will be modelled using an E_{max} model. If the data warrant, the model will be a nonlinear mixed effect model for the parameters in the model. If convergence is not obtained with the E_{max} model, the E_{max} parameter may be fixed (assuming 100% reduction is possible) or a linear model will be considered. The parameter estimates for the model will be presented.

13. Interim Analysis

No interim PK or PD analysis is anticipated for this study

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PPD Biostatistics and Programming

Statistical Analysis Plan (SAP) Client Approval Form

Client:	ARMO Biosciences, Inc / Eli Lilly and Company
Protocol Number:	AM0010-801
Document Description:	Final Statistical Analysis Plan Amendment
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Date (DD-MMM-YYYY)

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