

Protocol: J1L-AM-JZGE/AM0010-801

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

NCT03267732

Approval Date: 10-Aug-2017



CLINICAL STUDY PROTOCOL

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

Sponsor: ARMO BioSciences, Inc.
575 Chesapeake Drive
Redwood City, CA 94063

Investigational Product: AM0010, PEGylated Recombinant Human Interleukin 10 (PEG-rHuIL-10)

IND No.: 117767

Protocol ID: AM0010-801

ARMO BioSciences
Medical Monitor

Protocol Version/Date: Original 10 August 2017

PPD

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PROTOCOL APPROVAL

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

AM0010-801

Approval of protocol by sponsor:

PPD

Chief Medical Officer

08-10-2017

Date

PROTOCOL SYNOPSIS

Study Title:	A Phase 1 Study to Evaluate the Pharmacokinetics of Single and Multiple Doses of AM0010 in Healthy Adult Subjects
Sponsor	ARMO BioSciences, Inc.
Investigational Product	AM0010 (pegilodecakin)
Name of Active Ingredient	PEG-rHuIL-10
Study Centers Planned:	One research center in the United States
Number of Subjects Planned:	Approximately 24 subjects (n=12 per cohort) will be enrolled in this study. At least 5 males and 5 females enrolled at each dose level.
Target Population:	Healthy adult subjects.
Objectives:	<p>Primary Objective:</p> <ul style="list-style-type: none"> To characterize the pharmacokinetics (PK) of AM0010 after single and multiple subcutaneous (SQ) injections in healthy adult subjects. <p>Secondary Objective:</p> <ul style="list-style-type: none"> To evaluate the safety of single and multiple SQ doses of AM0010 in healthy adult subjects.
Study Design:	<p>The study is an open-label, single followed by multiple dose study to evaluate the PK / PD of AM0010 in healthy adult subjects. The primary objective of this study is to characterize the PK of AM0010 after single and multiple SQ injections. The secondary objective is to evaluate the safety of single and multiple AM0010 SQ doses of AM0010. Subjects will receive a single SQ injection of AM0010 and, followed for 72 hours with PK sampling (serum) at multiple time points. Subjects will then receive AM0010 at the assigned dose SQ qd x 6 and have PK / PD samples collected at multiple time points between injections as well as after the final injection of AM0010.</p> <p>Two dose levels (5 µg/kg and 10 µg/kg) will be evaluated with 12 subjects enrolled at each dose level. AM0010 at 5 µg/kg will be administered as one of two 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 patient'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 patient's weight during the course of the study.</p> <p>Primary and Secondary Endpoints:</p> <p><u>Primary:</u></p> <p>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), half-life ($t_{1/2}$).</p> <p><u>Secondary:</u></p> <p>Incidence of adverse events, injection site reactions, clinically relevant changes in laboratory values, EKGs, and vital signs.</p>

Duration of Treatment:	Single AM0010 SQ injection with a 72- hour wash out followed by AM0010 SQ qd x 6 (total of 7 SQ injections)
Study Eligibility Criteria:	<p>Summary of Subject Eligibility Criteria:</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male or female between 18 and 55 years of age, inclusive. 2. Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures. 3. Must have a body mass index (BMI) between 19 and 32 (kg/m²) at study Screening. 4. Must be HIV negative by HIV 1/0/2 testing. 5. Must be Hepatitis B (HBV) surface antigen negative. 6. Must be Hepatitis C (HCV) antibody negative. 7. Must have a creatinine clearance (CL_{Cr}) ≥ 80 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight as measured at the Screening evaluation, i.e., Male: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = \text{CL}_{Cr} \text{ (mL/min)}$ Female: $\frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})} = \text{CL}_{Cr} \text{ (mL/min)}$ 8. Females must have a negative serum pregnancy test. 9. Females of childbearing potential (as defined in Section 10.5) must agree to utilize protocol recommended highly effective contraception methods from Screening throughout the duration of study treatment and for 30 days following the last dose of study drug. 10. Male subjects must agree to utilize a highly effective method of contraception during vaginal intercourse throughout the study period and for 90 days following discontinuation of investigational medicinal product. 11. Male subjects must refrain from sperm donation from Day 0 through completion of the study and continuing for at least 90 days from the date of last dose of study drug. 12. Must refrain from blood donation from 30 days prior to Day 0 through completion of the study and continuing for at least 30 days from date of last dose of study drug. 13. Must, in the opinion of the Investigator, be in good general health based upon medical history, physical examination (including vital signs), and Screening laboratory evaluations (hematology and chemistry must fall within the laboratory's reference normal ranges unless the results have been determined by the Investigator to have no clinical significance). 14. Must have either a normal 12-lead electrocardiogram (EKG) with PR interval ≤210 ms and QTcF interval ≤450 ms/males or ≤470 ms/females, or one with abnormalities that are considered clinically insignificant by the Investigator. 15. Must be willing and able to comply with all study requirements.

<p>Study Eligibility Criteria continued:</p>	<p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Pregnant or lactating subjects. 2. Have any serious or active medical or psychiatric illness that, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment. 3. Have previously participated in an investigational trial involving administration of any investigational compound within 30 days prior to the study dosing. 4. Current alcohol or substance abuse judged by the Investigator to interfere with subject compliance. 5. Have poor venous access and are unable to donate blood. 6. Have donated blood ≥ 300 mL within 30 days of study dosing. 7. Have donated plasma within 7 days of study dosing. 8. Have taken any prescription medications including low dose steroids or over-the-counter medications, including herbal products, within 28 days of commencing study drug dosing with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications. 9. Have history of significant drug sensitivity or drug allergy. 10. Have a history of significant serious skin disease such as, but not limited to, rash or eruptions, food allergy, eczema, psoriasis, or urticaria. 11. Have a history or family history of Long QT Syndrome, Wolfe-Parkinson-White Syndrome, or have a family history of sudden cardiac death or unexplained death in an otherwise healthy individual between the ages of 1 and 40 years. 12. Have been vaccinated within 90 days of study dosing. 13. Known hypersensitivity to the study drugs, the metabolites, or formulation excipients. 14. Have active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). 15. Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months of study screening, or expected to receive these agents during the study (e.g., corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies). 16. History of syncope, palpitations, or unexplained dizziness. 17. Have an implanted defibrillator or pacemaker. 18. Are unable to comply with study requirements. 19. Are believed, by the study Investigator, to be inappropriate for study participation for any reason.
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**Study
Procedures/
Frequency:**

Procedures:

Within 28 days prior to first dose (Day 1) and after informed consent has been obtained, subjects who have been identified by Investigators will be screened to establish eligibility. All screening procedures and tests establishing eligibility will be performed as summarized in the Schedule of Events ([Appendix 2](#)).

Twenty-four subjects will be randomly assigned in a 1:1 ratio to two dose levels of AM0010 (5 µg/kg and 10 µg/kg). AM0010 at 5 µg/kg will be administered as one of two 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 patient'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 patient's weight during the course of the study.

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 labs, vital signs, 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 pre-dose, and subjects will then receive a SQ injection of AM0010. On the morning of Days 4–9, 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/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 ([Appendix 2](#)).

Serum PK / PD samples will be collected throughout the study as detailed in the table below:

Dose	Day(s)	PK Timepoints	PD Timepoints
1	1-4	Pre-dose, 1, 2, 4, 8, 12, 16, 24, 36, 48, and 60 hrs after Dose 1	Pre-dose, 4, 12, 24 and 48 hrs after Dose 1
2	4	Pre-dose, 2, 4, 8, 12 hrs after Dose 2	Pre-dose - Dose 2
3	5	Pre-dose	Pre-dose - Dose 3
4	6	Pre-dose, 4 and 8 hrs after Dose 4	Pre-dose - Dose 4
5	7	Pre-dose	Pre-dose - Dose 5
6	8	Pre-dose	Pre-dose - Dose 6
7	9-12	Pre-dose, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hrs after Dose 7	Pre-dose, 4, 12, 24, 48, and 72 hrs after Dose 7

NOTE:

PK blood draws ± 5 minutes from timepoints

PD blood draws ± 15 minutes from timepoints

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**Statistical
Methods:**

Descriptive statistics including means, medians, standard deviations, and ranges will be calculated for continuous variables, and categorical data will be summarized using frequency counts and percentages.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine transaminase
AM0010	PEGylated Recombinant Human Interleukin 10
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AUC	Area under the serum concentration over time curve
BMI	Body mass index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Clearance
CL _{Cr}	Creatinine clearance
C _{max}	Maximum drug concentration
CR	Complete response
CRC	Colorectal cancer
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
EC ₁₀	10% effective concentration
EkG	Electrocardiogram
EOS	End of Study
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
HBV	Hepatitis B
hCG	Human chorionic gonadotropin
HCV	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HSP	Hysterosalpingogram
ICF	Informed Consent Form

ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IUD	Intra-uterine device
LDH	Lactate dehydrogenase
LFT	Liver function test
MedDRA®	Medical Dictionary for Regulatory Activities
NHP	Non-human primates
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung carcinoma
ORR	Overall response rate
PDAC	Pancreatic cancer
PEG-rHuIL-10	PEGylated recombinant form of human IL-10
PK	Pharmacokinetics
PR	Partial response
qd	Latin: quaque die (once a day)
QRS	QRS interval
QT	QT interval
QTcF	QT interval corrected for heart rate by Fridericia's formula
RBC	Red blood cell
RCC	Renal cell carcinoma
rHuIL-10	Recombinant Human Interleukin 10
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAER	Serious Adverse Event Report
SQ	subcutaneous
SOP	Standard Operating Procedure
$t_{1/2}$	Half Life
TK	Toxicokinetics
T_{max}	Time of maximum concentration observed
WBC	White blood cell
β -hCG	Beta-Human Chorionic Gonadotropin

1.0 OBJECTIVES

1.1 Primary

To characterize the pharmacokinetics (PK) after single and multiple subcutaneous (SQ) doses of AM0010 in healthy adult subjects.

1.2 Secondary

To evaluate the safety of single and multiple SQ doses of AM0010 in healthy adult subjects.

2.0 ENDPOINTS

2.1 Primary Endpoints

PK parameters including maximum drug concentration (C_{max}), area under the serum concentration over time curve (AUC), Clearance (Cl), half-life ($t_{1/2}$).

2.2 Secondary Endpoints

Incidence of adverse events, injection site reactions, clinically relevant changes in laboratory values, EKGs, and vital signs.

3.0 BACKGROUND AND RATIONALE

3.1 Background on AM0010

AM0010 is a PEGylated recombinant form of human IL-10 (PEG-rHuIL-10) CCI

[REDACTED]

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.

3.1.1 Pharmacology

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Further details on the pre-clinical pharmacology of AM0010 can be found in the Investigator's Brochure.

3.1.2 Toxicology

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In summary, the non-clinical toxicology program for AM0010 supports the continuation of clinical trials in humans.

3.1.3 Pharmacokinetics

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Further details on the pre-clinical PK of AM0010 are shown in the Investigator's Brochure.

3.2 Clinical Trials of AM0010

3.2.1 Phase 1 Safety Study of AM0010 in Patients with Advanced Solid Malignancies

In a previous First-in-Human study, preliminary exposure, safety, and efficacy data have been collected.

The previous dose escalation study defined the safety profile, maximum tolerated dose, recommended Phase 3 dose as monotherapy and in combination with chemotherapy, pharmacokinetics, and objective tumor responses (according to immune related response criteria) in patients with advanced solid malignancies.

In the previous study, 33 patients with advanced solid malignancies across several indications (melanoma, ovarian, pancreatic, prostate, renal cell, colorectal, non-small cell lung carcinoma [NSCLC]) were exposed to AM0010 as a single agent. Patients received doses from 1 µg/kg up to 40 µg/kg daily. Cohorts 1 through 6 (1 through 40 µg/kg) were found to be safe and tolerable.

Subsequently, clinical activity was further explored in 9 dose expansion cohorts with AM0010 monotherapy in specific disease indications such as cholangiocarcinoma, renal cell carcinoma (RCC), colorectal cancer (CRC), NSCLC, and pancreatic cancer (PDAC). Efficacy of AM0010 in combination with chemotherapy, targeted therapy, or immune checkpoint inhibitors was explored in 9 additional combination regimens (Table 1).

Table 1: Clinical Experience

Regimen (AM0010, qd)	Highest Daily Dose of AM0010 Administered	G3/4 AEs Related to Study Drugs	DCR/ORR (evaluable patients **)
Monotherapy	40 µg/kg *	thrombocytopenia, anemia, LFT, nausea (1 patient)	All: 47% / 5% (116) RCC: 66% / 27% (15) **
Platinum / Taxane	10 µg/kg *	thrombocytopenia, anemia, fatigue neutropenia	All: 74% / 35% (23)

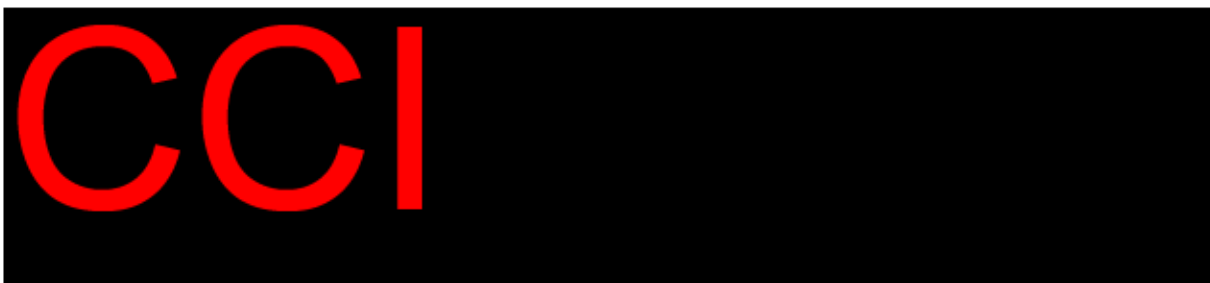
Regimen (AM0010, qd)	Highest Daily Dose of AM0010 Administered	G3/4 AEs Related to Study Drugs	DCR/ORR (evaluable patients **)
FOLFOX	5 µg/kg (RP2D) 10 µg/kg	Thrombocytopenia, neutropenia, leukopenia, anemia, fatigue, hyperbilirubinemia	All: 74% / 16% (31) PDAC: 87% / 20% (15) ***/****
Gemcitabine / nab-paclitaxel	5 µg/kg	anemia, neutropenia, thrombocytopenia, nausea, emesis	All: 100% / 20% (5)
Capecitabine	10 µg/kg	Thrombocytopenia, anemia, fatigue	PDAC 100% / 0% (5)
Paclitaxel (weekly)	10 µg/kg	Thrombocytopenia, anemia, neutropenia, fatigue	All: 30/0% (3)
Pazopanib	10 µg/kg	Thrombocytopenia, anemia, fatigue	RCC: 100% / 33% (3)
Pembrolizumab	10/20 µg/kg *	thrombocytopenia, anemia, hyponatremia, rash	All: 67% / 21% (43) NSCLC 100% / 40% (5) RCC 100% / 50% (8)
Nivolumab	20 µg/kg *	thrombocytopenia, anemia, rash	All: 68% / 31% (19) ****
Gemcitabine / Carboplatin	5 µg/kg*	thrombocytopenia, anemia, hyponatremia, rash	TNBC: 57% / 0% (7)

* found well tolerated by AM0010-001 investigators; ** escalation cohorts only; *** pancreatic cancer patients only; **** study in progress

Most patients enrolled in the escalation cohorts and first expansion cohort had previously progressed during or following multiple lines of therapy. Despite this fact, very encouraging objective tumor responses have been observed in most combination therapies with AM0010.

3.2.2 Clinical Pharmacokinetics of AM0010

CCI For the most current information on clinical PK, please refer to the current Investigator's Brochure.



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The current study AM0010-801 will provide additional PK data of AM0010 after single and multiple SQ injections in healthy adult subjects.

3.2.3 Dose Rationale

In the current study AM0010-801, the 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.

To align with the approach in the Phase 3 program, dosing of AM0010 will be weight stratified, and subjects at a particular dose level will be administered a fixed dose based on the subject's weight at Screening as described in [Section 7.1](#). For subjects who are ≤ 80 kg, the dose of AM0010 will be 400 µg and 800 µg at the 5 µg/kg and 10 µg/kg dose level, respectively. For subjects who are > 80 kg, the dose of AM0010 will be 800 µg and 1600 µg at the 5 µg/kg and 10 µg/kg dose level, respectively.

4.0 EXPERIMENTAL PLAN

4.1 Hypothesis

A formal hypothesis will not be tested. Analysis of PK and safety data will provide information that will guide future development of AM0010.

4.2 Study Design

The study is an open-label, single followed by multiple dose study to evaluate the PK of AM0010 in healthy adult subjects. The primary objective of this study is to characterize the PK of AM0010 after single and multiple SQ injections. The secondary objective is to evaluate the safety of single and multiple SQ doses of AM0010. 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 qd x 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.

4.3 Number of Centers

This study will be conducted at a single research center in the United States.

4.4 Number of Subjects

This trial is expected to enroll 24 healthy adult subjects at two dose levels (n=12/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.

4.5 Estimated Study Duration

4.5.1 Study Duration for Subjects

Including the 28-day screening period and the 14-day treatment and follow-up period, the subject participation time is approximately 42 days.

5.0 SUBJECT ELIGIBILITY

Investigators will maintain a screening log of all potential study candidates that includes limited information about the potential candidate (e.g., screening ID), date, and outcome of the screening process (e.g., enrolled into study, reason for ineligibility, or refused to participate).

5.1 Inclusion Criteria

To be eligible for this study, potential subjects must fulfill all of the following inclusion criteria:

1. Male or Female between 18 and 55 years of age, inclusive.
2. Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.
3. Must have a body mass index (BMI) between 19 and 32 (kg/m²) at study Screening.
4. Must be HIV negative by HIV 1/0/2 testing.
5. Must be Hepatitis B (HBV) surface antigen negative.
6. Must be Hepatitis C (HCV) antibody negative.
7. Must have a creatinine clearance (CL_{Cr}) ≥ 80 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight as measured at the Screening evaluation, i.e.,

$$\text{Male: } (140 - \text{age in years}) \times (\text{wt in kg}) = \text{CL}_{\text{Cr}} (\text{mL/min}) \\ 72 \times (\text{serum creatinine in mg/dL})$$

$$\text{Female: } (140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85 = \text{CL}_{\text{Cr}} (\text{mL/min}) \\ 72 \times (\text{serum creatinine in mg/dL})$$

8. Females must have a negative serum pregnancy test.
9. Females of childbearing potential (as defined in [Section 10.5](#)) must agree to utilize protocol recommended highly effective contraception methods from Screening throughout the duration of study treatment and for 30 days following the last dose of study drug.
10. Male subjects must agree to utilize a highly effective method of contraception during vaginal intercourse throughout the study period and for 90 days following discontinuation of investigational medicinal product.

11. Male subjects must refrain from sperm donation from Day 0 through completion of the study and continuing for at least 90 days from the date of last dose of study drug.
12. Must refrain from blood donation from 30 days prior to Day 0 through completion of the study and continuing for at least 30 days from date of last dose of study drug.
13. Must, in the opinion of the Investigator, be in good general health based upon medical history, physical examination (including vital signs), and Screening laboratory evaluations (hematology and chemistry must fall within the laboratory's reference normal ranges unless the results have been determined by the Investigator to have no clinical significance).
14. Must have either a normal 12-lead electrocardiogram (EKG) with PR interval ≥ 210 ms and QTcF interval ≤ 450 ms/males or ≤ 470 ms/females, or one with abnormalities that are considered clinically insignificant by the Investigator.
15. Must be willing and able to comply with all study requirements.

5.2 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for study participation:

1. Pregnant or lactating subjects.
2. Have any serious or active medical or psychiatric illness that, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment.
3. Have previously participated in an investigational trial involving administration of any investigational compound within 30 days prior to the study dosing.
4. Current alcohol or substance abuse judged by the Investigator to potentially interfere with subject compliance.
5. Have poor venous access and are unable to donate blood.
6. Have donated blood ≥ 300 mL within 30 days of study dosing.
7. Have donated plasma within 7 days of study dosing.
8. Have taken any prescription medications including low dose steroids or over-the-counter medications, including herbal products, within 28 days of

- commencing study drug dosing with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications.
9. Have history of significant drug sensitivity or drug allergy.
 10. Have a history of significant serious skin disease, such as but not limited to, rash or eruptions, food allergy, eczema, psoriasis, or urticaria.
 11. Have a history or family history of Long QT Syndrome, Wolfe-Parkinson-White Syndrome, or have a family history of sudden cardiac death or unexplained death in an otherwise healthy individual between the ages of 1 and 40 years.
 12. Have been vaccinated within 90 days of study dosing.
 13. Known hypersensitivity to the study drugs, the metabolites or formulation excipients.
 14. Have active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
 15. Have been treated with systemic steroids, immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening, or expected to receive these agents during the study (e.g., corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies).
 16. History of syncope, palpitations, or unexplained dizziness.
 17. Have an implanted defibrillator or pacemaker.
 18. Are unable to comply with study requirements.
 19. Are believed, by the study Investigator, to be inappropriate for study participation for any reason.

6.0 SUBJECT ENROLLMENT

All subjects must personally sign and date and receive a copy of the informed consent form (ICF) before any study specific screening procedures are performed.

All subjects who are enrolled and receive study medication will be identified by a unique subject number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study. A subject is considered enrolled when study medication is administered on Day 1.

6.1 Treatment Assignment

Subject eligibility will be established at the conclusion of the screening evaluations, and subjects will then be randomized in an open-label fashion to the 5 µg/kg or 10 µg/kg dose cohort.

6.2 Randomization

Randomization to 5 µg/kg or 10 µg/kg of AM0010 will be based on a randomization schedule prepared by ARMO BioSciences and/or designee 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.

7.0 TREATMENT PROCEDURES

7.1 Investigational Product Dosage, Administration, and Schedule

AM0010 is provided by ARMO BioSciences. AM0010 is a sterile, clear solution formulated at 2 mg/mL (Table 3).

Table 3: AM0010 Dose Formulation

Component	Concentration
AM0010	2 mg/mL



The AM0010 dose at the 5 µg/kg and 10 µg/kg dose level will be administered as one of two fixed doses based on the subject's weight at Screening (Table 4). For subjects who are ≤ 80 kg, the dose of AM0010 will be 400 µg and 800 µg at the 5 µg/kg and 10 µg/kg dose level, respectively. For subjects who are > 80 kg, the dose of AM0010 will be 800 µg and 1600 µg at the 5 µg/kg and 10 µg/kg dose level, respectively.

Table 4: 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

Details of preparing and administering all study products are included in the Pharmacy Binder provided by ARMO BioSciences prior to the start of the study.

7.2 Compliance in Investigational Product Administration

All study investigational product administration will occur under medical supervision and must comply with protocol-specified criteria. Complete drug accountability records must be maintained. All records and unused supplies of the investigational product must be available for inspection during monitoring visits for the conduct of AM0010 investigational product accountability.

7.3 Other Protocol-Required Drugs

AM0010 will be the only investigational product used in this study.

7.4 Overdose

A dose known to have been taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol, misuse or abuse of study drugs, whether suspected or confirmed, and whether or not associated with an adverse experience, must be reported to ARMO BioSciences or if applicable, the CRO. Any questions or concerns will be discussed with the Medical Monitor.

Overdose will be considered a serious adverse event (SAE) only if any of the seriousness criteria are met. Any clinical sequelae in association with the overdose will be reported as an adverse event (AE) (or SAE, as appropriate) along with the overdose. Details of signs or symptoms, clinical management, and outcome will be reported, if available.

7.5 Individual Subject Stopping Rules

An individual subject may be discontinued at the discretion of the Investigator and the Sponsor due to clinically significant findings including but not limited to adverse events, clinical laboratory abnormalities, or physical examination findings. Subjects may also be discontinued for hospitalization or disease exacerbation, in the opinion of the Investigator.

If a subject experiences Grade 2 anemia or thrombocytopenia or other Grade 3 toxicities (regardless of relationship to AM0010), treatment will be postponed until the toxicity is resolved to Grade 1 (as defined by the CTCAE, v 4.03), mild, or returns to the subject's baseline value.

A subject experiencing AM0010-related Grade 4 toxicities will not receive additional AM0010 treatment and will be followed until resolution of toxicity. Subjects withdrawn or withheld from AM0010 treatment will be treated as deemed appropriate by the Investigator.

Subjects who withdraw early will be encouraged to remain in the study for safety follow-up, and assessments will continue to be obtained as scheduled. Otherwise, EOS procedures will be performed and the appropriate case report forms (CRFs) will be completed.

For subjects who discontinue AM0010 and are willing to remain on study, continued collection of safety data and PK / PD samples is encouraged. Specifically, if a subject discontinues treatment after receiving Dose 1, follow-up to Day 4 including the 72 hour PK sampling on the morning of Day 4 will occur. If a subject discontinues treatment at any time during Doses 2–7, procedures that correspond to time points from Days 9 –12 will occur with the procedures on Day 9 corresponding to the day of the last injection of AM0010.

If an unscheduled interruption of AM0010 occurs, the study site will notify ARMO BioSciences at the earliest possible time. In the event that a subject requires an unscheduled interruption of AM0010 under conditions other than those described in this section, the case will be reviewed by ARMO BioSciences to determine whether such a subject will be allowed to resume AM0010 treatment.

7.6 Dose Adjustment

No intra-subject dose adjustments will be allowed.

7.7 Excluded Therapy

The following medications are excluded while subjects are participating in the study:

- Any prescription medications including low dose steroids or over-the-counter medications, including herbal products, with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications. However, the short term use of topical hydrocortisone cream or A&D ointment to treat minor skin irritation will be allowed. If a subject requires use of a disallowed medication, a request for such use must be reviewed by the Sponsor, and if approved, subjects may continue to participate in the study.
- Any and all illegal or illicit drug use including use of prescription drugs outside the care of the prescribing physician.

8.0 STUDY PROCEDURES

8.1 Screening

Within 28 days prior to first dose (Day 1) and after informed consent has been obtained, subjects who have been identified by the Investigator based on clinical history will be screened to establish eligibility. All screening procedures and tests establishing eligibility will be performed as summarized in the Schedule of Events ([Appendix 2](#)).

The following evaluations and procedures will be performed within 28 days from Day of dosing except as noted:

- Written informed consent
- Physical Examination
- Clinical evaluations:
 - Medical history, including demographics
 - Weight and height
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead EKG – single
- Safety laboratory assessments:
 - Hematology
 - Serum chemistry
 - HBV and HCV Serology
 - HIV 1/0/2 Testing
 - Serum pregnancy test
 - Urinalysis
 - Urine drug screen
- Concomitant medications

8.2 Treatment

The following procedures will be conducted after subject eligibility has been established.

8.2.1 Day 0 / Baseline

The following procedures and assessments will be performed on Day 0/Baseline:

- Admission to inpatient research facility
- Clinical evaluation:
 - Physical Exam
 - Weight (calculate dose from this weight)
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead EKG – triplicate
- Safety laboratory assessments:
 - Hematology
 - Serum chemistry
 - Serum pregnancy test
 - Urinalysis
 - Urine drug screen
- Concomitant medications (throughout the day)

8.2.2 Day 1

The following procedures and assessments will be performed on Day 1:

Pre-dose: Day 1

- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead EKG – single
- Pre-dose PK / PD sample – Day 1

Administer AM0010 SQ injection #1

Post-dose: Day 1

- PK and PD blood draws (please refer to [Table 5](#))
- 12-Lead EKG – single at 8 and 12 hours after SQ injection #1
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

8.2.3 Day 2

The following procedures and assessments will be performed on Day 2:

- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

8.2.4 Day 3

The following procedures and assessments will be performed on Day 3:

- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

8.2.5 Day 4

The following procedures and assessments will be performed on Day 4:

Pre-dose: Day 4

- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead EKG – single
- Concomitant medications
- Adverse events
- PK and PD blood draws (please refer to [Table 5](#))

Administer AM0010 SQ injection #2

Post-dose: Day 4

- PK and PD blood draws (please refer to [Table 5](#))
- 12-Lead EKG – single at 8 and 12 hours after SQ injection #2
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

8.2.6 Day 5

The following procedures and assessments will be performed on Day 5:

Pre-dose: Day 5

- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

Administer AM0010 SQ injection #3

8.2.7 Day 6

The following procedures and assessments will be performed on Day 6:

Pre-dose: Day 6

- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead EKG – single
- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

Administer AM0010 SQ injection #4

Post-dose: Day 6

- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

8.2.8 Day 7

The following procedures and assessments will be performed on Day 7:

Pre-dose: Day 7

- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

Administer AM0010 SQ injection #5

8.2.9 Day 8

The following procedures and assessments will be performed on Day 8:

Pre-dose: Day 8

- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

Administer AM0010 SQ injection #6

8.2.10 Day 9

The following procedures and assessments will be performed on Day 9:

Pre-dose: Day 9

- 12-Lead EKG – single
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

Administer AM0010 SQ injection #7

Post-dose: Day 9

- PK and PD blood draws (please refer to [Table 5](#))
- 12-Lead EKG – single at 8 and 12 hours after SQ injection #7
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

8.2.11 Day 10

The following procedures and assessments will be performed on Day 10:

- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

8.2.12 Day 11

The following procedures and assessments will be performed on Day 11:

- PK and PD blood draws (please refer to [Table 5](#))
- Concomitant medications (throughout the day)
- Adverse events (throughout the day)

8.2.13 Day 12

The following procedures and assessments will be performed on Day 12:

- PK and PD blood draws (please refer to [Table 5](#))
- Safety laboratory assessments:
 - Hematology
 - Serum Chemistry
- Concomitant medications
- Adverse events
- Discharge from inpatient research facility

8.2.14 Day 15 / End of Study (EOS)

The following procedures and assessments will be performed on Day 15 / EOS:

- Physical Exam including weight
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-Lead EKG – single
- Concomitant medications
- Adverse events
- Safety laboratory assessments
 - Hematology
 - Serum chemistry
 - Serum pregnancy test
 - Urinalysis

8.3 Subjects Residency

Subjects will be admitted to the research site on Day 0 and will remain resident until completion of study-related procedures on Day 12. The Day 15/EOS visit to the research site will be on an outpatient basis for subsequent PK / PD draws, safety assessments, and safety blood draw time points outlined in the Schedule of Events ([Appendix 2](#)).

8.4 PK / PD Sample Collection

PK / PD samples will be collected throughout the study as detailed in [Table 5](#) below:

Table 5: PK / PD Sample Collection

Dose	Day(s)	PK Timepoints	PD Timepoints
1	1-4	Pre-dose, 1, 2, 4, 8, 12, 16, 24, 36, 48, and 60 hrs after Dose 1	Pre-dose, 4, 12, 24 and 48 hrs after Dose 1
2	4	Pre-dose, 2, 4, 8, 12 hrs after Dose 2	Pre-dose - Dose 2
3	5	Pre-dose	Pre-dose - Dose 3
4	6	Pre-dose, 4 and 8 hrs after Dose 4	Pre-dose - Dose 4
5	7	Pre-dose	Pre-dose - Dose 5
6	8	Pre-dose	Pre-dose - Dose 6
7	9-12	Pre-dose, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hrs after Dose 7	Pre-dose, 4, 12, 24, 48, and 72 hrs after Dose 7

NOTE:

PK blood draws $\pm$ 5 minutes from timepoints

PD blood draws $\pm$ 15 minutes from timepoints

8.5 Medical and Concomitant Medication History

A complete medical and concomitant medication history will be obtained by the Investigator or designee. Medical history will include information on the subject's significant past medical events (e.g., prior hospitalizations or surgeries), any concurrent medical illness, and concomitant medications including prescription, non-prescription medications, vitamins, and minerals taken up to 28 days before study Day 1. The medical history findings and concomitant medications will be recorded on the CRF page.

8.6 Physical Examination

The Investigator or qualified designee will perform a physical examination at Screening, Days 0/Baseline and Day 15 as outlined in the Schedule of Events ([Appendix 2](#)). Pre-dose abnormal findings will be reported on the medical history page of the CRF. Any changes from Day 0 pre-dose (baseline) physical examination which represent a clinically significant deterioration will be documented on the adverse events page of the CRF.

Height (in centimeters and without shoes) and weight (in kg and without shoes) will be obtained at Screening.

8.7 Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, oral and temperature, will be measured by the Investigator or qualified designee at the time points listed in the Schedule of Events ([Appendix 2](#)). Subjects must be seated or in a semi-recumbent position for at least 5 minutes prior to vital signs measurement. All measurements will be recorded on the appropriate CRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as adverse events, if appropriate.

8.8 Electrocardiogram

12-lead EKGs reporting ventricular rate, PR, QRS, QT, and QTcF intervals will be obtained by the Investigator or designee at the time points listed in the Schedule of Events ([Appendix 2](#)). Baseline EKGs will be performed in triplicate on Day 0 after admission to the inpatient research facility. Single EKGs will be performed at all other time points. Subjects will be seated, semi-recumbent, or supine for at least 5 minutes before the EKG is obtained. The Investigator or qualified designee will review the EKG. The original EKG tracings will be maintained in the source documentation of each subject and the appropriate data reported on the CRF.

8.9 Adverse Events and Concomitant Medications

Subjects will be assessed for adverse events ([Section 10.1.1](#)) and concomitant medication(s) during each visit as outlined in the Schedule of Events ([Appendix 2](#)). Any AEs or concomitant medication use reported throughout the study will be recorded in the CRF with appropriate source documentation.

8.10 Laboratory Safety Tests

Blood samples for local laboratory safety tests (clinical chemistry and hematology) will be collected according to the Schedule of Events ([Appendix 2](#)). The date and time of blood collection will be recorded in the subject's source documentation. The tests will be analyzed using standard procedures. White blood cell differentials will be reported as absolute counts. All laboratory tests must be reviewed by the Investigator or qualified designee. Additional safety laboratory assessments may be performed if clinically indicated.

The following analytes will be tested (see [Table 6](#)):

Table 6: 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 (CL_{cr})/glomerular filtration rate will be calculated based on the Cockcroft-Gault formula using actual body weight: CL_{cr} (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

Urine samples will be collected for urinalysis and urine drug screen according to the Schedule of Events ([Appendix 2](#)). The date and time of urine collection will be recorded in the subject's source documentation. The following analytes will be tested (see [Table 7](#)). Urine microscopic evaluation will only be performed if an abnormal urine dipstick result is observed.

Table 7 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

8.11 Other Screening Laboratory Tests

All females will have a serum pregnancy test at Screening, on Day 0 and on Day 15/EOS. The results must be confirmed as negative in order for the subject to be eligible for the study.

8.12 Blood Volume

It is anticipated that subjects enrolled in this study will agree to provide whole blood for safety and PK / PD assessment during their participation in this study as listed in [Table 8](#).

Table 8: Approximate Total Blood Volume between Screening and Day 15

Procedure	Volume per Collection, mL	Number of Collections	Total Volume, mL
Laboratory safety (chemistry + hematology + serology)	5	9	45
PK / PD serum sample collection	4 (2/2)	32	128
TOTAL			173

Note: PK and PD blood draws may have timepoints that overlap, whereby 1 x 4mL tube may be used. For PK only timepoints, a smaller tube may be used, decreasing the total mL volume. PK timepoints total 32 and PD timepoints total 16

9.0 REMOVAL AND REPLACEMENT OF SUBJECTS

9.1 Removal of Subjects

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. The Investigator and ARMO BioSciences also have the right to withdraw a subject from the study at any time for any reason.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any subject may withdraw full consent to participate in the study at any time during the study. The Investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health.

Withdrawal of partial consent means that the subject does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on study (e.g., participate in all subsequent study visits or procedures). Subjects may decline to continue receiving investigational product at any time during the study. These subjects, as well as those who have stopped receiving investigational product for other reasons (e.g., Investigator or Sponsor concern) will continue the schedule of study observations for 7 days post last injection.

For subjects who discontinue AM0010 and are willing to remain on study, follow-up visits to collect safety data and PK samples are encouraged. Specifically, if a subject discontinues treatment after receiving Dose 1, follow-up to Day 4 including the 72-hour PK sampling on the morning of Day 4 will occur. If a subject discontinues treatment at any time during Doses 2–7, follow-up visits that correspond to time points from Days 9–12 will occur with the procedures on Day 9 corresponding to the day of the last injection of AM0010.

The reason for withdrawal will be recorded on the study completion CRF page. If the subject is withdrawn due to an adverse event, the Investigator will arrange for the subject to have follow-up visits until the adverse event has resolved or stabilized.

Reasons for removal from investigational product or observation may include:

- Withdrawal of consent
- Study is terminated
- Change in subject eligibility
- Significant protocol deviation
- Subject noncompliance
- Adverse event (report on adverse event CRF page)
- Other as specified by the Investigator

Should a subject request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

10.0 SAFETY DATA COLLECTION, RECORDING, AND REPORTING

10.1 Definitions

10.1.1 Adverse Events (AE)

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 (ICH E2A II/A/1, 21 CFR 312.32).

10.1.2 Serious Adverse Events

A serious adverse event 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (ICH E2A/II/B, 21 CFR 312.32).

10.2 Reporting Procedures for All Adverse Events

The Investigator is responsible for ensuring that all adverse events (as defined in [Section 10.1.1](#) and as further specified below) observed by the Investigator or reported by subjects are collected and recorded in the subjects' medical records, in the CRF, and, for serious adverse events, on the serious adverse event report (SAER) form. The principal

method of collection of adverse events will be through interview with study subjects. These adverse events will include the following:

- All serious adverse events (as defined in [Section 10.1.2](#)) that occur after the subject has signed the informed consent form
- All non-serious adverse events (as defined in [Section 10.1.1](#)) that occur after first receipt of investigational product through the end of the study

The following adverse event attributes must be assigned by the Investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to investigational product; and action taken. The Investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or CRF pages.

Investigators are required to assess whether there is a reasonable possibility that the investigational product caused or contributed to an AE.

Many terms and scales are used to describe the degree of causality between an investigational product and an event. There is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A, III/A/1).

Determination of whether there is a reasonable possibility that an investigational product caused or contributed to an AE includes assessing temporal relationships, biologic plausibility, dechallenge / rechallenge information (if available), association (or lack of association) with underlying disease, and presence (or absence) of a more likely cause.

The relationship to study drug therapy will be assessed using the following definitions:

Not Related: Evidence exists that the adverse event has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

Related: A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state or concomitant

therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

Medically significant adverse events considered related to the investigational product by the Investigator or the Sponsor will be followed until resolved or considered stable. All serious adverse events will be followed until resolution or until the Investigator and Sponsor both judge the event to be chronic or stable.

The Investigator will classify the intensity of an adverse event on the case report forms. Specific criteria for the intensity of adverse events are described in the Common Terminology Criteria for Adverse Events v 4.03 (CTCAE: National Cancer Institute) grades (Grades 1 to 5).

If a CTCAE term is not available for the AE/SAE, the severity will be graded using Grade 1 through Grade 5 as defined in the CTCAE definitions.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe (Grade 3) reaction is not necessarily a serious reaction.

For adverse events that do not meet the criteria for dose holding outlined in [Section 7.5](#) (Individual Subject Stopping Rules), it will be left to the Investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. Subject should be under medical supervision until symptoms cease or the condition becomes stable.

10.3 Serious Adverse Event Reporting Procedures

10.3.1 Responsibilities of the Investigator

In the event that any serious adverse events (see [Section 10.1.2](#)) occur during this study or within the follow-up period, the Investigator will notify ARMO BioSciences or designee via phone immediately (within 24 hours) after becoming aware of the incident (see [Table 9](#)).

Table 9: ARMO BioSciences Drug Safety Contact Information

ARMO BioSciences Drug Safety	PPD
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The Investigator will simultaneously email the SAE Report Form and other required documentation to ARMO BioSciences. The Investigator will promptly provide follow-up information requested by ARMO BioSciences. All serious adverse events will be followed until resolution or the Investigator and Sponsor both judge the event to be chronic or stable. Detailed instructions for reporting SAEs are included in the Regulatory Binder.

10.3.2 Sponsor Responsibilities

ARMO BioSciences or its designee will report serious adverse events to the FDA.

10.4 Risks for Women of Childbearing Potential or During Pregnancy

The risks of treatment with AM0010 during pregnancy have not been evaluated. If females utilize hormonal agents as one of their contraceptive methods, the same hormonal method must have been used for at least 3 months before study dosing.

Pregnancy must be excluded before the start of treatment with AM0010 and prevented thereafter by reliable contraceptive methods. Serum pregnancy test will be performed at Screening, on Day 0 and on Day 15/EOS. The results must be confirmed as negative in order for the subject to be eligible for the study.

10.5 Definition of Female of Childbearing Potential

For the purposes of this study, a female subject of childbearing potential is a non-menopausal female who has not had a tubal sterilization, hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

Women will be considered to be post-menopausal if they have an oophorectomy or they have 12 months of spontaneous amenorrhea with FSH >40 mIU/mL regardless of age.

10.6 Contraception Requirements for Female Subjects

Female subjects of childbearing potential who engage in vaginal intercourse must agree to utilize protocol-recommended methods of contraception from signing of informed consent throughout the study period and for 30 days following the last dose of study drug. Study subjects who are not sexually active must have periodic confirmation of continued abstinence from vaginal intercourse and all females must have regular pregnancy testing while taking AM0010. The investigator/designee will counsel for avoiding pregnancy in case subject chooses to engage in vaginal intercourse.

Protocol-recommended contraceptive methods are: (1) a combination of one hormonal method and one barrier method; (2) two barrier methods where one method is the male condom; or (3) use of an IUD or tubal sterilization (see [Table 10](#) below). Acceptable hormonal methods include: injectable progesterone, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring. Acceptable barrier methods include: diaphragm (with spermicide) and the male condom. Female subjects must use either a hormonal method or a barrier method if the partner has a vasectomy. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNG 20 IUD inserted, no other contraception is needed.

If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after micro-insertion. Prior to verification, Essure is not considered a reliable form of contraception, and the contraception methods described below must be used. Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing.

All females must have negative serum β -hCG at screening. Lactating females must discontinue nursing before investigational medicinal product administration.

Table 10: Protocol-Recommended Contraceptive Methods

Methods to Use by Themselves	Combination Methods	
	Hormone Methods (choose one and use with a barrier method)	Barrier Methods (use both OR choose one and use with a hormone method)
Intra-uterine devices (IUDs) <ul style="list-style-type: none"> • Copper T 380A IUD • LNG 20 IUD Tubal sterilization	Estrogen and Progesterone <ul style="list-style-type: none"> • Oral contraceptives • Transdermal patch • Vaginal ring Progesterone <ul style="list-style-type: none"> • Injection • Implant 	<ul style="list-style-type: none"> • Diaphragm with spermicide • Male condom (with or without spermicide)
	Partner's vasectomy must be used along with a hormone or barrier method.	

10.7 Additional Requirements for Male Subjects

Male subjects must agree to use condoms during vaginal intercourse and avoid sperm donation while enrolled in the study and for at least 90 days after administration of the last dose of study medication.

10.8 Procedures to be Followed in the Event of Pregnancy

All females will have a serum pregnancy test at Screening, on Day 0, and on Day 15/EOS. The results must be confirmed as negative in order for the subject to be eligible for the study.

Subjects will be instructed to notify the Investigator if they become pregnant at any time during the study or if they become pregnant within 30 days of last study drug dose.

Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the Investigator and discontinue study drug immediately. The Investigator will report all pregnancies to ARMO BioSciences or designee within 24 hours of becoming aware of the pregnancy. The Investigator will counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

Monitoring of the subject will continue until the conclusion of the pregnancy. Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion for any reason) must be reported within 24 hours. The outcome will be reported to ARMO BioSciences or designee. If the end of the pregnancy occurs after the study has been

completed, the outcome will be reported directly to ARMO BioSciences Safety Group by email: PPD

Pregnancies of female partners of male study subjects exposed to ARMO BioSciences' study drug must also be reported, and relevant information will be submitted to ARMO BioSciences or designee within 24 hours. Monitoring of the subject will continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the ARMO BioSciences' Safety Group by email: PPD

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

The study is an open-label, single followed by multiple dose study to evaluate the PK / PD of AM0010 in healthy adult subjects. The primary objective of this study is to characterize the PK / PD of AM0010 after single and multiple SQ injections. The secondary objective is to evaluate the safety of single and multiple SQ doses of AM0010. Subjects will receive a single SQ injection of AM0010 and be followed for 72 hours with PK / PD sampling (serum) at multiple time points. Subjects will then receive AM0010 at the assigned dose SQ qd x6 and have PK / PD 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.

11.2 Study Endpoints

11.2.1 Primary Endpoint – Pharmacokinetics of AM0010

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), half-life ($t_{1/2}$).

11.2.2 Secondary Endpoint – Safety of AM0010

Incidence of adverse events, injection site reactions, clinically relevant changes in laboratory values, EKGs, and vital signs.

11.3 Sample Size Considerations

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.

11.4 General Methods of Data Analysis

No pre-specified hypothesis testing will be performed. Summary statistics will be provided. Descriptive statistics including means, medians, standard deviations, and ranges will be calculated for continuous variables, and categorical data will be summarized using frequency counts and percentages.

11.5 Demographic and Safety Data

Demographic variables include: age, sex, ethnicity, and race. Other baseline characteristics include height, weight, body mass index, and medical history. Demographic and baseline characteristics will be summarized by treatment group.

11.6 Clinical Safety Data

Safety variables to be summarized include vital signs, adverse events, and clinical laboratory results (hematology and chemistry).

Vital signs (including heart rate, diastolic blood pressure, systolic blood pressure, and temperature) will be summarized in terms of observed values and changes from baseline.

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will present by preferred term the frequency and percentage of subjects reporting each observed event with onset on or after initiation of study medication.

Laboratory data will be summarized in terms of observed values, changes from baseline, and values relative to normal ranges. Listings will flag laboratory values that are outside of normal range.

11.7 Pharmacokinetics Data Analysis

Summary statistics (mean, standard deviation, minimum, maximum, n, and coefficient of variation) will be calculated for serum concentrations of AM0010 at each time point. Individual and mean AM0010 serum concentration vs. time curves will also be generated.

Pharmacokinetic parameter values will be estimated. A non-compartmental model will be used to generate parameter estimates, provided there are sufficient data to permit calculations. Pharmacokinetic parameters to be calculated include C_{max} , T_{max} , AUC, CI, and $t_{1/2}$. AUC_{0-t} (where t = time of the last sample on the pharmacokinetic profile in which quantifiable drug was detected) and $AUC_{0-\infty}$ will be estimated using trapezoidal calculation.

One- and two-compartment linear models with first-order absorption will be evaluated. Absorption rates, absorption lag, and relative bioavailability will be allowed to differ between dose levels. Inter-individual variability will initially be permitted for all structural parameters with covariance between relevant parameters. If graphics suggest that the proposed

models are not appropriate (e.g., non-linear pharmacokinetics, the need for a different absorption model, or time-related changes in apparent clearance), other models will be considered. Model selection will be guided by changes in the objective function (using the likelihood ratio test) and goodness-of-fit plots. The effect of covariates (e.g., body size, gender, age, race, organ function) will be incorporated into the model if supported statistically. The analysis will be conducted with the NONMEM system (Icon Development Solutions, Hanover, MD), version 7.3 or later.

Summary statistics (i.e., mean, standard deviation, median, minimum, maximum, n, and coefficient of variation) will be presented for all pharmacokinetic parameters.

11.8 Biomarker Data Analysis

Immune related cytokines in the serum will be analyzed to understand the pharmacodynamic response to AM0010

12.0 ETHICS

12.1 Institutional Review Board (IRB)

This study will be conducted in accordance with the US Code of Federal Regulations governing the protection of human subjects (21 CFR 50), Institutional Review Board (IRB), the obligations of clinical Investigators (21 CFR 312) and the ICH document "Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance," dated April 1996.

The Protocol and Informed Consent that will be used must be approved by the Investigator's IRB before the study is initiated. Documentation of this approval signature and the date of the IRB approval is to be provided to the study Sponsor (ARMO BioSciences, Inc.).

The Sponsor expects the Investigator to comply with local IRB requirements. The Investigator will also comply with current standards of Good Clinical Practice (GCP), particularly in reference to the safety and rights of the subjects. Investigators are encouraged to discuss any ethical issues that arise prior to or during the conduct of the study with the Sponsor.

12.2 Ethical Conduct of the Study

This study will be conducted in compliance with GCP according to the US Code of Federal Regulations (21 CFR), International Conference on Harmonisation (ICH) guidelines, and local ethical and legal requirements that are consistent with the most current version of the Declaration of Helsinki.

12.3 Informed Consent

The Informed Consent must comply with all applicable US Code of Federal Regulations (21 CFR 50), the Health Insurance Portability and Accountability Act (HIPAA) if required, and the ICH document "Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance," dated April 1996. It should also include any additional information required by local laws relating to institutional review.

A statement that subject medical records must be available for investigations into serious adverse events must be included in the Informed Consent Form. It should also include any additional information required by local laws relating to institutional review.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed informed consent form should be retained in the subject's source record, and a copy of the signed consent form should be provided to the subject.

Written informed consent and HIPAA authorization (if required) will be obtained from all study subjects prior to any tests or evaluations as required by the institution and applicable regulations. A copy of the signed informed consent will be provided to each subject and will also be maintained in the subject's medical record.

13.0 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for complying with all local, state, and federal regulations relating to performing clinical research with an investigational product. The Investigator is responsible for ensuring that the investigation is conducted according to the signed Investigator Agreement (Form FDA 1572), the approved protocol, and applicable regulations for protecting the rights, safety, and welfare of study subject under the Investigator's care. The Investigator is additionally responsible for the control of investigational product and for providing accurate and verifiable data to the Sponsor.

The Investigator must obtain the Informed Consent and HIPAA authorization (if required) of each subject before participation in the study. The Investigator must assure initial and continuing review of the study by an IRB that complies with applicable national and local regulations.

The Investigator will maintain minutes of meetings with study staff and document training of research study personnel for conduct of the study, including qualifications, experience, and study role.

Other Investigator responsibilities relative to the IRB include the following:

- Submit to the IRB for review any advertisements that will be used to recruit subjects
- Submit all protocol amendments, revisions of the Investigator's Brochure, or revisions of the Informed Consent to the IRB for review
- If ARMO BioSciences notifies the Investigator about serious adverse events reported in other studies associated with this investigational product, report that information to the IRB
- Provide the IRB with any other information it requests before or during the conduct of the study
- Report to the IRB all adverse drug reactions that are serious, unexpected, and possibly or probably related to investigational product
- Maintain a file of study-related information
- Update the IRB on a minimum of a yearly basis

13.1 Investigator's Brochure and Standard Operating Procedures

The Investigator will be given a copy of the most current version of the Investigator's Brochure and appropriate SOPs for all laboratory procedures. The Investigator is obligated to become familiar with all sections of these documents prior to initiation of the study.

13.2 Informed Consent and HIPAA (if required)

The Investigator is responsible for the content of the Informed Consent and HIPAA authorization, with approval by the Sponsor.

The Investigator (or properly qualified designee) is responsible for obtaining Informed Consent and HIPAA authorization from each study subject participating in the study. All pertinent aspects of the study must be explained to the study subject before he/she signs the Informed Consent and HIPAA authorization. Informed Consent and HIPAA authorization must be obtained from the subject before any activity or treatment is undertaken which is not part of routine care. This includes but is not limited to the performance of diagnostic or therapeutic procedures and the administration of the investigational product. The subject must be informed that their medical records must be made available for investigation of adverse events and serious adverse events.

13.3 Study Initiation

Before the investigational product can be shipped to the study site and before the study can begin, the following documents must be submitted and received by the Sponsor:

- Original Form FDA 1572, signed by the Principal Investigator
- Documentation of the IRB approval of the protocol and Informed Consent
- A copy of the IRB-approved Informed Consent and HIPAA authorization that will be used
- Copy of current curriculum vitae and medical licenses of the Principal Investigator
- Investigator's financial disclosure form
- A membership list of the IRB

The Sponsor will notify the site when the study can begin.

13.4 Data Handling and Record Keeping

The Investigator must maintain a file for each subject that includes the signed Informed Consent and Investigator copies of all CRFs completed for that subject.

13.5 Study Documentation and Archive

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and EKG result reports, pharmacy records, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from ARMO BioSciences and/or applicable regulatory authorities.

In addition, all original source documents supporting entries on the case report forms must be maintained and be readily available.

No study documents will be destroyed without prior written agreement between ARMO BioSciences and the Investigator. Should the Investigator wish to assign the study records to another party and/or move them to another location, he/she must notify ARMO BioSciences in writing of the new responsible person and/or the new location.

13.6 Audits and Inspections

The Investigator will make source documents for this study available to appropriately qualified personnel from the Quality Assurance Unit or its designees or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

13.7 Monitoring the Study

It is understood that the responsible monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study (CRFs and other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements.

The monitor is responsible for inspection of the CRFs at regular intervals throughout the study, verification of the adherence to the protocol, and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigator (and his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.8 Confidentiality of Trial Documents and Subject Records

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, subjects will not be identified by their names but by an identification code. The Investigator should keep a subject enrollment log relating codes to the names of subjects. The Investigator should maintain documents not for submission to ARMO BioSciences, e.g., subjects' written consent forms, in strict confidence.

13.9 Retention of Data

Data related to this study must be stored according to the regulations pertaining to studies performed under an IND (21 CFR §312.62[c]).

An Investigator shall retain records required to be maintained under this part (case histories and data collected as part of this trial for all study subjects) for a period of 2 years following the date a marketing application is approved for the drug for the indications for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

14.0 SPONSOR RESPONSIBILITIES

ARMO BioSciences, Inc. is the Sponsor for this study. PPD M.D., Ph.D. will oversee these activities and serve as a Medical Monitor.

14.1 Sponsor Contact Information

SPONSOR

ARMO BioSciences, Inc.
575 Chesapeake Drive
Redwood City, CA 94063

MEDICAL MONITOR

PPD M.D., Ph. D.
575 Chesapeake Drive
Redwood City, CA 94063

PPD

15.0 APPENDICIES

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by ARMO BioSciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

PPD

Principal Investigator Name (Printed)

Signature

Date 11 Aug 2017

PPD

Appendix 2: Schedule of 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	X																		
Vital signs ^b	X	X														Pre Dose					
12-lead EKG ^c	X	X3 ^g						X	X										X	X	
Concomitant Medication	<div></div>																				
Adverse Events Review				<div></div>																	
Confinement at Study Center		<div></div>																			
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		<div></div>										Pre Dose	<div></div>				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 semi-recumbent position for at least 5 minutes.

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

^d Safety lab tests are outlined in [Table 6](#).

^e Serum pregnancy testing in all females.

^f Urine lab tests are outlined in [Table 7](#).

^g X3 = Triplicate EKGs

Appendix 2: Schedule of Events (Cont'd)

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					Pre										X	
12-lead EKG ^c	Dose					Dose			X	X						X	
Concomitant Medication	<div><div></div></div>																
Adverse Events Review	<div><div></div></div>																
Confinement at Study Center	<div><div></div></div>															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	<div><div></div></div>			Pre	Pre	Pre	<div><div></div></div>									
PD Blood Draws	Dose			Dose	Dose	Dose		X		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 semi-recumbent position for at least 5 minutes.

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

^d Safety lab tests are outlined in [Table 6](#).

^e Serum pregnancy testing in all females.

^f Urine lab tests are outlined in [Table 7](#).