Clinical Study Protocol J1L-AM-JZGF, AM0010-802

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

NCT03381547

Approval Date: 30-Oct-2017

CLINICAL STUDY PROTOCOL

Study Title:	An Open Label, Randomized, Single Dose, 3-Way Crossover Study to Evaluate the Pharmacokinetics of Different Dose Levels and Dose Formulations of AM0010 in Healthy Adult Subjects
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:	AM0010-802
ARMO BioSciences Medical Monitor	Name: PPD Telephone: PPD
Protocol Version/Date:	Original 30 October 2017

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PROTOCOL APPROVAL

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

AM0010-802

Approval of protocol by sponsor:

PPD

10.31.17

Date

PROTOCOL SYNOPSIS

Study Title:	An Open Label, Randomized, Single Dose, 3-Way Crossover Study to Evaluate the Pharmacokinetics of Different Dose Levels and Dose Formulations of AM0010 in Healthy Adult Subjects
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 12 subjects will be enrolled in this study. At least 4 males and 4 females enrolled.
Target Population:	Healthy adult subjects.
Objectives:	Primary Objective: • To characterize the pharmacokinetics (PK) of different dose levels and dose formulations of AM0010 after single subcutaneous (SQ) injections in healthy adult subjects. Secondary Objective: • To evaluate the safety of single SQ injections of AM0010 in healthy adult subjects.
Study Design:	The study is an open-label, randomized, single dose, 3-way crossover study to evaluate the PK of different dose levels and dose formulations of AM0010 in healthy adult subjects. The primary objective of this study is to characterize the PK of two dose levels and two dose formulations of AM0010 after single SQ injections. The secondary objective is to evaluate the safety of single SQ injections of AM0010. Two dose levels, 0.8 (1.6) mg and 0.4 (0.8) mg and two dose formulations (4 mg/mL and 2 mg/mL) will be evaluated in a 3-way crossover in 12 subjects.

Dose levels, Weight Brackets and Formulation of AM0010

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

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

Subjects will be randomized to one of three sequences:

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

Study Endpoints:	Primary: 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 ($t_{½}$). Secondary: Incidence of adverse events, injection site reactions, clinically relevant changes in laboratory values, and vital signs.
Duration of dosing:	Single AM0010 SQ injections (days 1, 8 & 15) with a 168-hour washout between each dose.
Study Eligibility Criteria:	Summary of Subject Eligibility Criteria: 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 19.0 and 32.0 (kg/m^2) 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: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = CL_{Cr}$ (mL/min) Female: $\frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})} = CL_{Cr}$ (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 dosing 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 (i.e. blood bank or blood donation center) 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 (ECG) 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.

Study Eligibility Criteria continued:

Exclusion Criteria:

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 dosing/PK, 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 smoked or used tobacco/nicotine products within 90 days prior to the study dosing.
6. Have poor venous access and are unable to donate blood.
7. Have donated blood ≥300 mL within 30 days of study dosing.
8. Have donated plasma within 7 days of study dosing.
9. 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.
10. Have history of significant drug sensitivity or drug allergy.
11. Have a history of significant serious skin disease such as, but not limited to, rash or eruptions, food allergy, eczema, psoriasis, or urticaria.
12. 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.
13. Have been vaccinated within 90 days of study dosing.
14. Known hypersensitivity to the study drugs, the metabolites, or formulation excipients.
15. 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).
16. 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).
17. History of syncope, palpitations, or unexplained dizziness.
18. Have an implanted defibrillator or pacemaker.
19. Are unable to comply with study requirements.
20. Are believed, by the study Investigator, to be inappropriate for study participation for any reason.

Study Procedures:

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 Assessments (Appendix 2).

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

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

For each dosing/PK period, subjects will be admitted to an inpatient research facility on the day prior to dosing and remain in residence until 72 or 168 hours after dosing.

- Period 1: PK Days 1-3, D/C Day 4
- Period 2: PK Days 8-10 D/C Day 11
- Period 3: PK Days 15-17 D/C Day 18. Return to research facility for Day 22 outpatient visit, PK (168 hour) and End of Study Procedures.

Baseline procedures including physical examination, safety labs, vital signs, and pregnancy tests (in all females) will be performed. Prior to dosing on the morning of Days 1, 8 and 15, a sample for PK will be drawn pre-dose, and subjects will then receive a SQ injection of AM0010.

The subjects will be discharged from the inpatient research facility Days 4, 11, and 18 after completion of study-related procedures. Schedule of Assessments (Appendix 2).

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

Dose	Day(s)	Timepoints
1	1-3	Pre-dose, 2, 4, 8, 12, 16, 24, 36, 48 and 72 hrs after Dose 1
2	8-10	Pre-dose, 2, 4, 8, 12, 16, 24, 36, 48 and 72 hrs after Dose 2
3	15-17 & 22	Pre-dose, 2, 4, 8, 12, 16, 24, 36, 48 , 72, and 168 hrs after Dose 3

Test Product, and Storage:

CCI [redacted]

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
Cl	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
D/C	Discharge
DCR	Disease control rate
EC_{10}	10% effective concentration
EcG	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
$t_{½}$	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) of different dose levels and dose formulations of AM0010 after single subcutaneous (SQ) injections in healthy adult subjects.

1.2 Secondary

To evaluate the safety of single SQ injections of AM0010 in healthy adult subjects.

2.0 ENDPOINTS

2.1 Primary Endpoints

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 ($t_{½}$).

2.2 Secondary Endpoints

Incidence of adverse events, injection site reactions, clinically relevant changes in laboratory values, 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

CCI [redacted]

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

3.1.2 Toxicology

CCI [redacted]

CCI [redacted]

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

3.1.3 Pharmacokinetics

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

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)
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.

CCI

CCI

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CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

3.2.3 Study Rationale

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

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, randomized, single dose, 3-way crossover study to evaluate the PK of different dose levels and dose formulations of AM0010 in healthy adult subjects. The primary objective of this study is to characterize the PK of two dose levels and two dose formulations of AM0010 after single SQ injections. The secondary objective is to evaluate the safety of single SQ injections of AM0010.

Two dose levels and two dose formulations (4 mg/mL and 2 mg/mL) will be evaluated in a 3-way crossover in 12 subjects. The two dose levels are assigned in two weight brackets, with subjects at or below 80kg in the lower bracket and subjects with more than 80kg body weight in the higher bracket.

AM0010 SQ doses of Dose A, Dose B, and Dose C will be administered as indicated in the Table 3.

Table 3 Dose levels, Weight Brackets and Formulation of AM0010

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

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

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

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

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

4.5 Estimated Study Duration

4.5.1 Study Duration for Subjects

Including the 28-day screening period and the 21-day dosing and follow-up period, the subject participation time is approximately 49 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 19.0 and 32.0 (kg/m^2) 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: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = \text{CLCr (mL/min)}$

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

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 dosing/PK 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 (i.e. blood bank or blood donation center) 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 (ECG) 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 which, in the opinion of the Investigator, would interfere with subject dosing/PK, 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 smoked or used tobacco/nicotine products within 90 days prior to the study dosing.
6. Have poor venous access and are unable to donate blood.
7. Have donated blood ≥300 mL within 30 days of study dosing.
8. Have donated plasma within 7 days of study dosing.

9. 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.
10. Have history of significant drug sensitivity or drug allergy.
11. Have a history of significant serious skin disease, such as but not limited to, rash or eruptions, food allergy, eczema, psoriasis, or urticaria.
12. 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.
13. Have been vaccinated within 90 days of study dosing.
14. Known hypersensitivity to the study drugs, the metabolites or formulation excipients.
15. 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).
16. 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).
17. History of syncope, palpitations, or unexplained dizziness.
18. Have an implanted defibrillator or pacemaker.
19. Are unable to comply with study requirements.
20. 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 drug is administered on Day 1.

6.1 Dose Administration 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 one of three sequences.

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

6.2 Randomization

Randomization to one of the three sequences 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 1:1:1 ratio. At least 4 males and 4 females will be enrolled.

After subjects have completed the screening procedures and are confirmed to be eligible for the study, they will be randomized to 1 of 3 sequences.

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

7.0 AM0010 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 and 4 mg/mL (Table 4).

Table 4: AM0010 Dose Formulation

Component	Concentration
AM0010	2 mg/mL and 4 mg/mL
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CCI [redacted]

The AM0010 dose and formulation will be administered as one of three dose administration assignments (Table 3).

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), dosing 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 dose and will be followed until resolution of toxicity. Subjects withdrawn or withheld from AM0010 dosing, 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 samples is encouraged.

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 dosing.

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 Assessments (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 ECG – 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

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

8.2 Baseline Days 0, 7 & 14

- Admission to inpatient research facility
- Clinical evaluation:
  - Physical Exam
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- Safety laboratory assessments:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test
  - Urinalysis
  - Urine drug screen
- Concomitant medications

8.3 Dosing and PK Period 1 (Days 1 - 4)

- **Day 1**
  - Pre-dose:
    - Vital signs (pulse, blood pressure, respiratory rate, and temperature)
    - PK sample collection
  - Dosing SQ injection AM0010
  - Post-dose:
    - PK sample collection at 2, 4, 8, 12, and 16 hours (± 15 mins) after SQ injection AM0010
  - Concomitant medications
  - Adverse events

- **Day 2**
  - PK sample collection at 24, 36 and 48 hours (± 15 mins) after SQ injection AM0010
  - Concomitant medications
  - Adverse events

- **Day 3**
  - PK sample collection at 72 hours (± 30 mins) after SQ injection AM0010
  - Concomitant medications
  - Adverse events

- **Day 4**
  - Discharge from inpatient research facility

8.4 Dosing and PK Period 2 (Days 8 - 11)

- **Day 8**
  - Pre-dose:
    - Vital signs (pulse, blood pressure, respiratory rate, and temperature)
    - PK sample collection
  - Dosing SQ injection AM0010
  - Post-dose:
    - PK sample collection at 2, 4, 8, 12, and 16 hours (± 15 mins) after SQ injection AM0010
  - Concomitant medications
  - Adverse events

- **Day 9**
  - PK sample collection at 24, 36 and 48 hours (± 15 mins) after SQ injection AM0010
  - Concomitant medications
  - Adverse events

- **Day 10**
  - PK sample collection at 72 hours (± 30 mins) after SQ injection AM0010
  - Concomitant medications
  - Adverse events

- **Day 11**
  - Discharge from inpatient research facility

8.5 Dosing and PK Period 3 (Days 15 – 17 & 22)

- **Day 15**
  - Pre-dose:
    - Vital signs (pulse, blood pressure, respiratory rate, and temperature)
    - PK sample collection
  - Dosing SQ injection AM0010
  - Post-dose:
    - PK sample collection at 2, 4, 8, 12, and 16 hours (± 15 mins) after SQ injection AM0010
  - Concomitant medications
  - Adverse events

- **Day 16**
  - PK sample collection at 24, 36 and 48 hours (± 15 mins) after SQ injection AM0010
  - Concomitant medications
  - Adverse events

- **Day 17**
  - PK sample collection at 72 hours (± 30 mins) after SQ injection AM0010
  - Concomitant medications
  - Adverse events

- **Day 18**
  - Discharge from inpatient research facility

8.6 Day 22 / End of Study (EOS) Outpatient Visit

- Physical Exam
- Vital signs (pulse, blood pressure, respiratory rate, and temperature)
- 12-lead ECG – single
- Concomitant medications
- Adverse events
- Safety laboratory assessments
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Urine pregnancy test
  - Urine drug screen
  - PK sample collection at 168 hours (± 2 hours) after SQ injection AM0010

8.7 Subjects Residency

For each dosing/PK period, subjects will be admitted to an inpatient research facility on the day prior to dosing and remain in residence until 72 or 168 hours after dosing.

- Period 1: PK Days 1-3, D/C Day 4
- Period 2: PK Days 8-10 D/C Day 11
- Period 3: PK Days 15-17 D/C Day 18.
- Return to research facility for Day 22 outpatient visit, PK (168 hour) and End of Study Procedures.

8.8 PK Sample Collection

PK samples will be collected throughout the study as detailed in Table 5 below:

Table 5: PK Sample Collection

Dose	Day(s)	Timepoints
1	1-3	Pre-dose, 2, 4, 8, 12, 16, 24, 36, 48 and 72 hrs after Dose 1
2	8-10	Pre-dose, 2, 4, 8, 12, 16, 24, 36, 48 and 72 hrs after Dose 2
3	15-17 & 22	Pre-dose, 2, 4, 8, 12, 16, 24, 36, 48, 72, and 168 hrs after Dose 3

8.9 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.

8.10 Physical Examination

The Investigator or qualified designee will perform a physical examination at Days 0 and 15 as outlined in the Schedule of Assessments (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.

8.11 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 Assessments (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.

8.12 Electrocardiogram

12-lead ECGs 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 Assessments (Appendix 2). Single ECGs will be performed at specified time points. Subjects will be seated, semi-recumbent, or supine for at least 5 minutes before the ECG is obtained. The Investigator or qualified designee will review the ECG. The original ECG tracings will be maintained in the source documentation of each subject and the appropriate data reported on the CRF.

8.13 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 Assessments (Appendix 2). Any AEs or concomitant medication use reported throughout the study will be recorded in the CRF with appropriate source documentation.

8.14 Laboratory Safety Tests

Blood samples for local laboratory safety tests (clinical chemistry and hematology) will be collected according to the Schedule of Assessments (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
Sodium Potassium Chloride Bicarbonate Glucose BUN/Urea Creatinine [a] LDH ALT AST GGT Alkaline phosphatase Total bilirubin Amylase Total protein Albumin Calcium Magnesium Phosphate	Red Blood Cell (RBC) Count White Blood Cell (WBC) Count Hemoglobin Hematocrit Reticulocyte counts Platelet Count Differential Neutrophils Lymphocytes Monocytes	Anti-HCV Antibody Hepatitis B Surface Antigen HIV 1/0/2 Testing

; 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 Cockroft-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 Assessments (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	Amphetamine
pH	Cocaine
Blood	Opiates
Protein	Benzodiazepines
Glucose	Barbiturates
Ketones	Methadone
Bilirubin	Alcohol/Ethanol
Urobilinogen	Cannabinoids
WBC	
RBC	
Epithelial Cells	
Bacteria	
Casts	
Crystals	

8.15 Other Screening Laboratory Tests

All females will have a pregnancy test(s) as outlined in the Schedule of Assessments. Serum pregnancy test at Screening, results must be confirmed as negative in order for the subject to be eligible for the study. Urine pregnancy testing, on Days 0, 7, 14 and 22.

8.16 Blood Volume

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

Table 8: Approximate Total Blood Volume between Screening and Day 22

Procedure	Volume per Collection, mL	Number of Collections	Total Volume, mL
Laboratory safety - Screening (chemistry + hematology + serology)	11	1	11
Laboratory safety – Baseline (Days 0, 7 & 14) (chemistry + hematology)	9	2	18
Laboratory safety – EOS (Day 22) (chemistry + hematology)	9	1	9
PK serum sample collection	4	31	124
		TOTAL	**162**

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 product 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, continued collection of safety data and PK samples until 7 days after the last AM0010 dosing is encouraged.

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 AM0010 dosing or from the study. A subject may also voluntarily withdraw from AM0010 dosing due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an EOS assessment and 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

	Phone	Email
ARMO BioSciences Drug Safety	PPD	PPD

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 AM0010 dosing 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 the study of dosing with AM0010 and prevented thereafter by reliable contraceptive methods. All females will have a pregnancy test(s) as outlined in the Schedule of Event. Serum pregnancy test at Screening, results must be confirmed as negative in order for the subject to be eligible for the study. Urine pregnancy testing, on Days 0, 7, 14 and 22.

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 heterosexually active must have periodic confirmation of continued abstinence from heterosexual 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 heterosexual/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) • Copper T 380A IUD • LNg 20 IUD Tubal sterilization	Estrogen and Progesterone • Oral contraceptives • Transdermal patch • Vaginal ring Progesterone • Injection • Implant	• 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 22/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, randomized, single dose, 3-way crossover study to evaluate the PK of different dose levels and dose formulations of AM0010 in healthy adult subjects. The primary objective of this study is to characterize the PK of two dose levels and two dose formulations of AM0010 after single SQ injections. The secondary objective is to evaluate the safety of single SQ injections of AM0010.

Two dose levels (0.8 mg and 0.4 mg) and two dose formulations (4 mg/mL and 2 mg/mL) will be evaluated in a 3-way crossover in 12 subjects. AM0010 SQ dose of 0.8 mg at 4 mg/mL (Dose A), 0.4 mg at 4 mg/mL (Dose B), and 0.4 mg at 2 mg/mL (Dose C) will be administered. Each dose will be separated by 7 days. After each single SQ injection of AM0010, subjects will be followed for 168 hours with PK sampling (serum) and safety evaluations at multiple time points.

Subjects will be randomized to one of three sequences:

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

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 ($t_{½}$).

11.2.2 Secondary Endpoint – Safety of AM0010

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

11.3 Sample Size Considerations

This trial with AM0010 is expected to enroll 12 subjects. At least 4 males and 4 females will enrolled. 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 dose 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, Cl, and $t_{½}$. 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.

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 ECG 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 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
575 Chesapeake Drive
Redwood City, CA 94063
PPD
PPD

15.0 APPENDICIES

Appendix 1: Investigator Signature Page

STUDY ACKNOWLEDGEMENT

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

AM0010-802

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.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2: Schedule of Assessments

Activities	Screening -28 to -1 Days	Baseline DAYS 0, 7 & 14	DAYS 1, 8 & 15		DAYS 1 - 3 and 8 - 10 and 15 - 17									DAY 22 EOS
			Pre Dose	SQ Injection	Hours Post Dose									
					2	4	8	12	16	24	36	48	72	168
GENERAL														
Informed Consent	X													
Clinical Evaluation [a]	X													
Physical Exam	X	X												X
Vital signs [b]	X	X	X											X
12-lead ECG [c]	X													X
Concomitant Medication	●	———	———	———	———	———	———	———	———	———	———	———	———	●
Adverse Events Review			●	———	———	———	———	———	———	———	———	———	———	●
Confinement at Study Center		●	———	———	———	———	———	———	———	———	———	———	———	●
Discharged From Unit												After 72 Hour PK		
LABORATORY ASSESSMENTS AND DOSING														
Hematology [d]	X	X												X
Serum Chemistry [d]	X	X												X
Urinalysis [f]	X	X												X
Urine Drug Screen [f]	X	X												X
HBV and HCV Serology	X													
HIV 1/0/2 Test	X													
Pregnancy Test [e]	Serum	Urine												Urine
AM0010 Dosing				X										
AM0010 PK Collection			X		●	———	———	———	———	———	———	———	———	●

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

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

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

[d] Safety lab tests are outlined in Table 6.

[e] Serum pregnancy testing in all females.

[f] Urine lab tests are outlined in Table 7.