A Phase 1, Randomized, Double-Blind, Multi-Site, Single Dose Escalation Study to Evaluate the Safety, Pharmacokinetics, and Immunogenicity of SAR440894 vs Placebo in Healthy Adults

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IND Sponsor: Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services

Draft or Version Number: 11.0

STATEMENT OF ASSURANCE

Each Institution will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protections (OHRP) for federally funded human subjects research. Each FWA will designate at least one Institutional Review Board (IRB)/Independent Ethics Committee (IEC) registered with OHRP, for which the research will be reviewed and approved by the IRB/IEC and will be subject to continuing review [45 CFR 46.103(b)]. The IRB/IEC designated under an FWA may include an institution's IRB/IEC, an independent IRB/IEC, or an IRB/IEC of another institution after establishing a written agreement with that other institution.

STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11 (Electronic Records and Electronic Signatures), and 21 CFR Part 312 (Investigational New Drug Application)
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry," published in the Federal Register (83 Federal Register 8882 [2018]).
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable Federal, State, and Local Regulations and Guidance
- Applicable DMID Policies, Guidelines, and Plans to include but not limited to: Clinical Quality Management Policy, DMID Guidelines for Clinical Study Product Management, Guidelines for Writing Notes to the Study File, Study Product Management Plan (SPMP), Clinical Quality Management Plan (CQMP), etc.

SIGNATURE PAGE

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of subjects.

Site Investigator Signature:

Signed: Date:

Principal Investigator Signature

Principal Investigator Printed Name

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LIST OF ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
AUC	Area Underneath the Plasma Concentration Versus Time Curve
AUC_{last}	Area Underneath the Plasma Concentration Versus Time Curve From Time 0 to the Last Quantifiable Concentration
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CHIKV	Chikungunya Virus
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum Observed Plasma Concentration
CMS	Clinical Material Services
CS	Clinically Significant
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination

FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
mAb	Monoclonal Antibody
MedDRA®	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MOP	Manual of Procedures
MRSD	Maximum Recommended Starting Dose
NCS	Not Clinically Significant
NHP	Non-human Primate
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
OHRP	Office for Human Research Protections

OTC	Over-the-counter
PBPK	Physiological Based Pharmacokinetic
PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SRC	Safety Review Committee
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWFI	Sterile Water for Injection
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time of the Maximum Observed Plasma Concentration
UP	Unanticipated Problem

PROTOCOL SUMMARY

Title: A Phase 1, Randomized, Double-Blind, Multi-Site, Single Dose Escalation Study to Evaluate the Safety, Pharmacokinetics, and Immunogenicity of SAR440894 vs Placebo in Healthy Adults

Design of the Study: This is a Phase 1, randomized, double-blind, multi-site, single dose escalation study to evaluate the safety, pharmacokinetic (PK), and immunogenicity of 5 dose levels of IV infusion SAR440894 vs placebo in healthy adults. Five cohorts (N=8 subjects each) will be randomized to SAR440894 (n=6) or placebo (n=2).

Single Ascending Dose Cohorts and Dose Regimens

Cohort	Dose	Number of subjects	
		SAR440894	**Placebo**
1	0.3 mg/kg	6	2
2	1 mg/kg	6	2
3	3 mg/kg	6	2
4	10 mg/kg	6	2
5	20 mg/kg	6	2
Total Number of Subjects		30	10
		40	

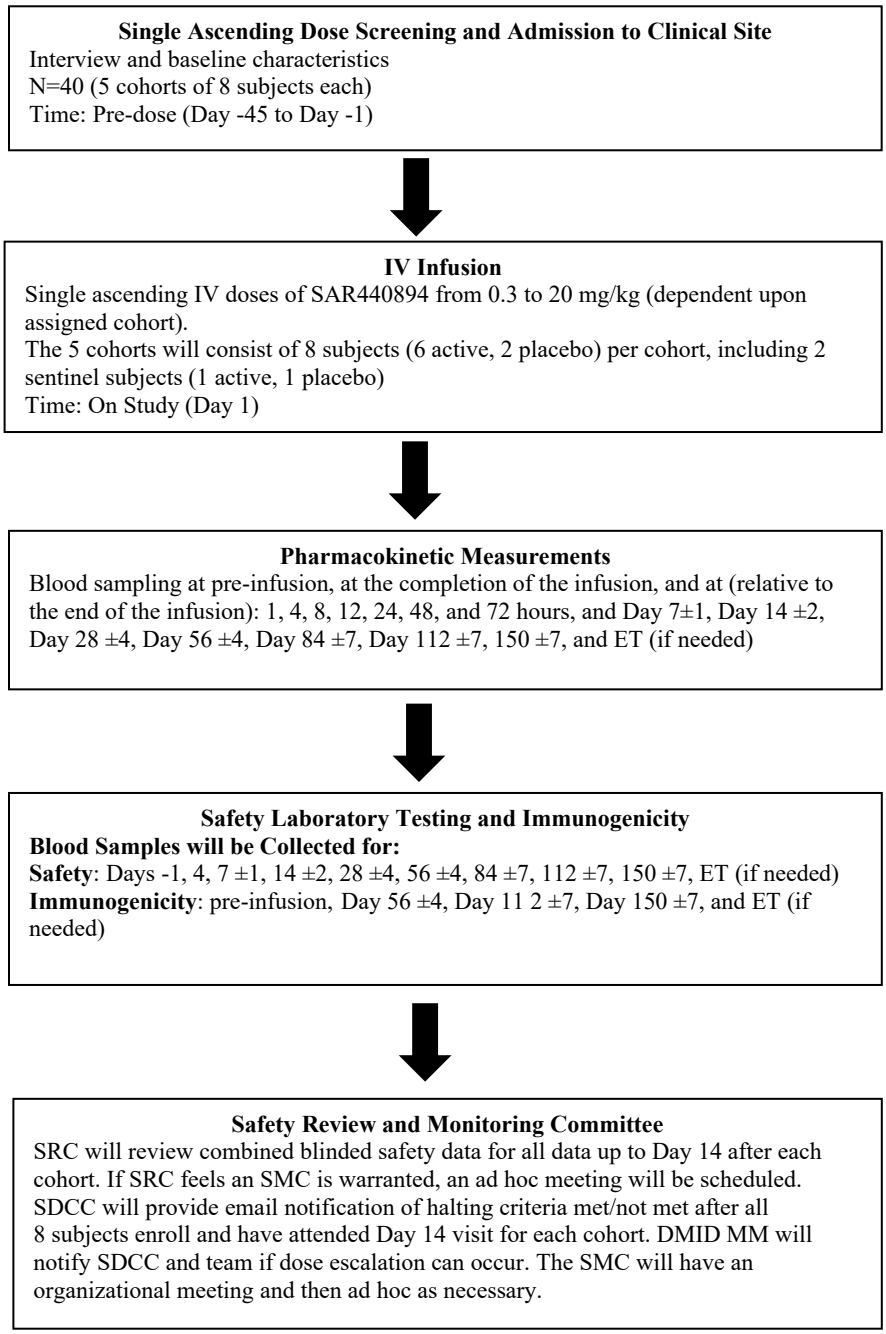
Study Phase: 1

Study Population: 40 healthy male and female subjects; aged 18-45 years inclusive; meeting eligibility criteria

Number of Sites: 3

Description of Study Product or Intervention:	• SAR440894 is a fully human monoclonal antibody (IgG1) directed against the E2 envelope protein of chikungunya virus (CHIKV). • SAR440894 will be supplied in glass vials that contain lyophilized powder consisting of active pharmaceutical ingredient (50 mg/mL), 10 mM histidine, 8% sucrose, 0.02% polysorbate 80 at pH of 5.5 after reconstitution with 2.3 mL SWFI (sterile water for injection). Extractable volume is 2 mL at 50 mg/mL (100 mg/vial). • Placebo will be supplied in glass vials that contain lyophilized powder consisting of 10 mM histidine, 8% sucrose, 0.02% PS80, at pH of 5.5. The lyophilized formulation will be reconstituted with 2.3 mL of sterile water for injection (SWFI). Extractable volume is 2 mL.
Study Objectives:	Primary: • To determine the safety of single ascending IV infusions of SAR440894 when administered in healthy adults. Secondary: • To determine the PK of single ascending doses of 60-minute IV infusions SAR440894 in healthy adults. • To assess the immunogenicity of single ascending doses of 60-minute IV infusions SAR440894 in healthy adults.
Duration of Individual Subject Participation:	Approximately 150 days (5 months), not including Screening visit (completed within 45 days prior to administration of study product)

Figure 1-1: Schematic of Study Design



1 KEY ROLES

This study is sponsored by DMID. Decisions related to this study will be made by the protocol team, which includes representatives from the participating clinical research sites (principal investigators [PIs]), DMID (sponsor), and Evotec. Key Roles are noted in the protocol-specific manual of procedures (MOP).

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background

Chikungunya virus (CHIKV) is a mosquito-transmitted virus with significant morbidity in humans, including arthritis persisting for months to years, and occasionally cardiac, gastrointestinal, ophthalmologic, and neurologic complications.[1] Chikungunya virus has affected over 60 countries, with major outbreaks over the past decade occurring in the Caribbean, Colombia, Bolivia, Brazil, Argentina, Kenya, Pacific Islands, and Pakistan.[1] Accordingly, epidemics of CHIKV are a sizable economic burden and impose a substantial strain on the operational capacities of local health care systems. There is currently no proven prophylactic or treatment against CHIKV, underscoring the public health need for drugs able to treat or prevent CHIKV infection.

SAR440894 is a potent, fully human monoclonal antibody (mAb) (IgG1) directed against the viral E2 envelope protein that has profoundly and rapidly reduced circulating and tissue viral levels in CHIKV-infected preclinical models. Due to its expected long terminal elimination half-life (approximately 4 weeks), SAR440894 has the potential for use both as a prophylactic treatment during CHIKV outbreaks and as a targeted therapy to reduce the progression to chronic symptoms in patients with acute CHIKV infections and disabling arthralgia. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), and immunogenicity of SAR440894 in healthy adult subjects.

Nonclinical Pharmacology and Toxicology

The safety of SAR440894 has been studied in in vivo toxicity studies including repeat dose studies (3 doses with a week interval between doses followed by a 5-week recovery period) in CD1 mice and non-human primates (NHPs), and the target organ identified was the kidney in CD1 mice.

Test article–related changes consisting of adverse renal tubular and interstitial inflammation (not dose-related in terms of incidence or severity) were seen in mice, at all doses tested, sacrificed 1 week after the last dose and were still present after 5 weeks of a recovery period. Therefore, a no observed adverse effect level (NOAEL) in CD1 mice was not identified.

In order to explore the etiology of these observations, two complementary studies were performed that included an assessment of off-target binding of SAR440894 on kidney samples from WT CD1 mice by IHC, and evaluation of immune reaction directed against SAR440894 and the formation of immune complexes. Both investigations were negative.

Based on the low incidence of findings in all mouse treatment groups, their lack of a clear dose/exposure-related trend in terms of incidence/severity, and the preserved functionality of the organ (no increases in blood urea nitrogen and creatinine levels), these findings are considered doubtful. In addition, this finding (test article–related changes consisting of adverse renal tubular and interstitial inflammation) can be strictly monitored in humans by evaluating blood and urine markers of renal function and injury.

There were no renal microscopic changes in the NHPs. However, mild to moderate, not dose-related, and transient increases in urine albumin/creatinine ratio and/or total protein/creatinine ratio were observed in the majority of males at the end of treatment. Based on the absence of a dose relationship, the presence in males only (despite no sex-related differences in terms of exposure), no decrease in serum albumin concentration, and no morphological changes, glomerular damage was ruled out. None of the findings were considered adverse, and the NOAEL was considered to be the top dose of 45 mg/kg, with a Day 15 mean area underneath the plasma concentration versus time curve from time 0 to the last quantifiable concentration (AUC_{last}) of 159,000 µg·h/mL and 153,000 µg·h/mL for males and females, respectively.

Pharmacology studies have been conducted in 2 CHIKV infected mouse models and 1 CHIKV infected NHP model to determine the therapeutic and prophylactic potential of SAR440894. SAR440894 demonstrated potent activity in the therapeutic approach. In mice, SAR440894 induced a significant reduction in the viral load in musculoskeletal tissues (> 1 log), a significant reduction in post-treatment viremia, and a significant reduction in footpad swelling, even when CHIKV was already disseminated in distal musculoskeletal tissues. In NHPs, SAR440894 administered IV efficiently controlled the development of CHIKV disease when administered at the highest doses of 2.5 and 12.5 mg/kg (viremia neutralization, decrease in CHIKV disease markers such as inflammatory markers).

SAR440894 also demonstrated a strong ability to protect animals from CHIKV infection when used as a prophylactic agent. In mice, SAR440894 administered intraperitoneally up to 21 days prior to CHIKV challenge induced a significant reduction of viral titer in the right hind limb at the site of virus injection and induced an effective reduction of footpad swelling. Prophylactic IV administration of SAR440394 at 0.5, 2.5, and 12.5 mg/kg in Rhesus Macaque 7 days prior to CHIKV infection controlled initial viremia and limited the inflammatory markers of CHIKV associated disease.

In mice receiving a 50 mg/kg IV bolus SAR440894, maximum observed plasma concentration (C_{max}) was 1230 µg/mL, clearance was 0.005 L/day/kg, and volume was 0.083 L/kg, with a half-life of 12.5 days. In NHP receiving a 2.5 mg/kg IV bolus, C_{max} was 75.7 µg/mL, clearance was 0.002 L/day/kg, and volume was 0.0706 L/kg, with a half-life of 25.5 days.

To evaluate the immunogenic potential of SAR440894, peripheral blood mononuclear cells from 22 healthy human donors were used to evaluate CD4 T-cell activation and cytokine release that may act as a potential prelude to development of anti-drug antibodies (ADA). Four of 22 donors responded to SAR440894 with a positive response from 1 cytokine (interferon gamma). No specific increase in immunogenicity potential was observed in the 16 donors with human leukocyte antigen alleles previously predicted to bind to a T-cell epitope. These results suggest that under the tested experimental conditions, SAR440894 did not seem to increase the risk of T-cell activation and overall, SAR440894 poses a low likelihood of immunogenicity.

No genotoxicity studies have been conducted with SAR440894 as the antibody is not expected to interact directly with DNA or other chromosomal material. In addition, no carcinogenicity studies have been performed because SAR440894 will not be used for long-term administration.

2.2 Scientific Rationale

2.2.1 Purpose of Study

The purpose of the study is to evaluate the safety, PK, and immunogenicity of 5 dose levels of IV infusion SAR440894 vs placebo in healthy adult subjects. No formal hypotheses are being tested in this Phase 1 study.

2.2.2 Rationale for Dosage and Dosing Regimen

There are no prior clinical studies completed with SAR440894. In mouse models with early infection, single doses between 0.5 to 12.5 mg/kg administered intraperitoneally demonstrated significant viral load reduction in musculoskeletal tissues and reduction of footpad swelling (ED50 of 0.75 mg/kg) and neutralization of viremia (1 mg/kg dose). In the same mouse model, SAR440894 still induced a significant reduction of the virus in musculoskeletal tissues at a dose of 2.5 mg/kg when administered later after infection (> 72 hours). Using CHIKV-infected NHP models, IV infusion for SAR440894 at dosages of 0.5 mg/kg, 2.5 mg/kg, and 12.5 mg/kg resulted in resolution of viremia at all dosages and absence of replicative virus in joints and tissues at the 2.5 mg/kg and 12.5 mg/kg dosage. Using the mouse and NHP in vivo efficacy models, the predicted effective therapeutic dose is 2.5 mg/kg and the predicted effective prophylactic dose is 1 mg/kg.

To determine the starting doses for the study, two approaches were used (physiological based pharmacokinetic [PBPK] modeling and single species allometry). The maximum recommended starting dose (MRSD) was chosen to give a target plasma area underneath the plasma concentration versus time curve (AUC) in humans that is $1/10^{th}$ the exposure level at the NOAEL from toxicity

studies in NHPs. Both approaches were also used to predict the clearance and dose that would result in the same target exposure level in CHIKV infected individuals.

A PBPK model for SAR440894 was constructed using the Simcyp minimal PBPK model for mAbs with 1:1 FcRn binding, and used the measured FcRn binding affinity as a model input. The resulting model for NHPs adequately captured the preclinical half-life and clearance with predicted values within 2-fold of the observed values. The predicted MRSD based on the human PBPK model was 0.83 mg/kg.

The MRSD was also predicted using single-species allometry using NHP data and allometric exponents of 0.5, 0.8, 0.9 and 1.1. The predicted MRSD was 0.29-1.79 mg/kg and the results from the PBPK model fall within this range. In totality, these results support a conservative MRSD of 0.29 mg/kg.

The proposed study design allows for accurate characterization of PK and safety while balancing the public health need to advance the development of this product by reducing the overall study timeline.

2.2.3 Study Population

In this study, healthy adult subjects that meet all eligibility criteria will be included in each cohort. As there are no prior clinical studies with SAR440894, a healthy adult population is considered appropriate for this first-in-human Phase 1 study. Non-pregnant women and minorities will be included in this study.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

This is the first clinical study of SAR440894 in humans. Nonclinical toxicology of SAR440894 is presented in Section 2.1. Although no significant risks to humans are anticipated due to the absence of human target, renal toxicity was observed in the mouse toxicity study consisting of adverse renal tubular and interstitial inflammation (not dose-related in terms of incidence or severity) at all doses. Based on the low incidence of findings in all treatment groups, their lack of a clear dose/exposure-related trend in terms of incidence/severity, and the preserved functionality of the organ (no increases in blood urea nitrogen and creatinine) levels, these findings are considered doubtful. While no clear mechanism of toxicity was identified in mice, a potential risk in humans remains.

The NHP study demonstrated a mild increase in total urine protein/creatinine ratio at 5 and 15 mg/kg, and a mild to moderate increase in urine albumin/creatinine ratio in males at 15 and 45 mg/kg. At 45 mg/kg, males also had a mild increase in incidence and severity of hematuria/hemoglobinuria. There were no renal microscopic changes observed in the cynomolgus monkey. Test item related changes observed in the urine were considered to be not adverse based on the 1) absence of a dose relationship, 2) the absence of morphological changes in the kidneys or urinary bladders (glomerular damage was ruled out), and 3) the transient effects (no changes were observed after 5 weeks of washout period). The NOAEL was considered to be the top dose of 45 mg/kg, with a Day 15 mean AUC_{last} of 159,000 µg·h/mL and 153,000 µg·h/mL for males and females, respectively.

As with other monoclonal antibodies, hypersensitivity reactions including anaphylaxis may occur immediately or within a few hours of infusion. This may be related to the generation of anti-drug antibody (ADA). However, such reactions are rare and often associated with mAbs targeted to human proteins. In preclinical testing, no ADA was detected in any SAR440894 animals. In addition, a life-threatening cytokine release syndrome occurred during a first-in-human study of a superagonist mAb; this was thought to occur due to the rapid release of proinflammatory cytokines from target immune cells.2 Because SAR440894 is a fully human antibody targeted toward viral proteins, we expect the risk of anaphylactic reactions and cytokine release syndrome will be very low. Other reactions are generally mild but may include fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia or chest pain.3

Delayed hypersensitivity and immune responses secondary to immune complex formation (ie, serum sickness) typically have a subacute presentation. As a result, the association between administration of a protein therapeutic and non-acute reactions may be more difficult to establish. Clinical signs may include delayed onset of fever, rash, arthralgia, myalgia, hematuria, proteinuria, serositis, central nervous system complications, and hemolytic anemia in the face of an ongoing antibody response to the protein therapeutic.

Other study-related risks include loss of confidentiality and complications from blood draws. The catheters inserted for blood draws could cause clotting, infection, or vein inflammation. The risks associated with insertion of the catheter and frequent blood draws are pain and bruising.

The benefit of the study is expected to outweigh the risk given the balance of the widespread prevalence of CHIKV, the morbidity associated with the disease, and the lack of available treatment with the reassuring nonclinical safety data.

2.3.2 Potential Benefits

There are no expected direct benefits to healthy subjects participating in this trial. The knowledge gained could be of benefit to public health, to individuals with CHIKV, and to individuals traveling to areas prone to outbreak.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

3.1 Study Design Description

This is a Phase 1, randomized, double-blind, placebo-controlled, multi-site, single dose escalation study to evaluate the safety, PK, and immunogenicity of 5 dose levels of IV SAR440894 vs placebo in healthy adults. The study is expected to enroll approximately 40 subjects.

Subjects in five cohorts (N=8 subjects each) will be randomized to SAR440894 (n=6) or placebo (n=2 [Table 3-1]). Randomization and masking procedures are described in detail in Section 10.3.1 and Section 10.3.2, respectively. Subjects will be screened and recruited into each cohort over 4 weeks prior to the start of the next cohort. Alternate subjects may be included in each cohort in order to facilitate study enrollment as described in Section 6.1.

In each cohort, 2 sentinel subjects will receive dosing (1 placebo, 1 active). The enrolling site PI(s) will review safety data through Day 4 to confirm no halting criteria (see Section 8.6.1) have been met and notify DMID MM prior to dosing the remaining subjects in the cohort. Upon approval from the DMID MM, the remaining subjects within each cohort will be dosed in groups of two at least 24 hours apart. Dosing start times will be staggered by at least 15 minutes between subjects. Subjects will remain in confinement for at least 72 hours after receiving study product. Thereafter, Follow-up in each cohort will occur until 150 ±7 days. This prolonged Follow-up period takes into account the long half-life of SAR440894 and will allow for appropriate characterization of the PK, safety, and immunogenicity of SAR440894. Accordingly, each cohort will complete the study approximately 22 weeks (150 days) from randomization through Follow-up.

Table 3-1: Single Ascending Dose Cohorts and Dose Regimens

Cohort	Dose	Number of Subjects	
		SAR440894	**Placebo**
1	0.3 mg/kg	6	2
2	1 mg/kg	6	2
3	3 mg/kg	6	2
4	10 mg/kg	6	2
5	20 mg/kg	6	2
Total Number of Subjects		30	10
		40	

All laboratory testing for Screening and safety monitoring will be performed at clinical site safety laboratories. After signature of the informed consent form (ICF), completion of the Screening visit, and confirmation of all eligibility criteria, the subject will be admitted to the clinical site 1 day before the dose of the study product. The site PI or medically qualified designee will be present at the time of study product administration and vital signs will be monitored per the study protocol (refer to the Schedule of Events, Appendix A, and Section 6.3). All subjects will remain in confinement from 1 day prior to administration of study product (Day -1) until at least 72 hours following dosing with SAR440894.

Blinded safety and clinical laboratory data up to the Day 14 visit will be evaluated by the Safety Review Committee (SRC) after each cohort. The safety review will include serious adverse events (SAEs), AEs, safety clinical laboratory results, electrocardiograms (ECGs), and vital signs. The SDCC will notify the SRC and study teams via email if any halting criteria have been potentially met after each cohort. If none of the predefined halting criteria are met, the DMID MM will provide approval for the study to proceed to the next cohort, or alternatively recommend convening of the Safety Monitoring Committee (SMC). If any of the predefined halting criteria are met, study enrollment and dosing will be stopped until the SMC provides recommendations regarding continuation of the study. Otherwise, the SMC will meet for an organizational meeting and ad hoc as appropriate. Dose-escalation halting rules are defined in Section 8.6.2. Review of SAR440894 time-concentration trends may occur following each cohort.

Study assessments (including the collection of AEs and SAEs) will be performed per the Schedule of Events by the study staff (Appendix A). All PK and anti-drug antibody samples will be shipped in accordance with the MOP and shipping will be monitored using Emmes GlobalTrace sample tracking system to the DMID Clinical Material Services (CMS), Fisher BioServices.

3.2 Study Objectives

3.2.1 Primary

- To determine the safety of single ascending IV infusions of SAR440894 when administered in healthy adults.

3.2.2 Secondary

- To determine the PK of single ascending doses of 60-minute IV infusions SAR440894 in healthy adults.
- To assess the immunogenicity of single ascending doses of 60-minute IV infusions SAR440894 in healthy adults.

3.3 Study Endpoints or Outcome Measures

3.3.1 Primary

- Occurrence of AEs and SAEs following the start of study product administration through the final visit (Day 150 [±7]), or Early Termination (ET).
- The occurrence of clinically significant (CS) changes from baseline in vital signs and clinical safety laboratory values following administration of study product through the final visit (Day 150 [±7]), or ET.
- The occurrence of CS changes in ECG parameters post administration of study product through the final visit (Day 150 [±7]), or ET.

3.3.2 Secondary

- SAR440894 PK after single ascending doses determined from plasma concentrations pre-dose and from the start of infusion until Day 150 (±7), or ET.
- SAR440894 immunogenicity determined from presence/absence of plasma human ADA and measurement of concentration from prior to infusion and at selected time points after infusion up to Day 150 (±7) or ET.

4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

4.1 Study Product Description

SAR440894 is a fully human mAb (Type IgG1) directed against the E2 envelope protein of CHIKV including mutations in the Fc part that improve binding to FcRn. The drug substance of SAR440894 is produced by cell culture (CHO cells), starting from a cGMP quality cell bank and purified via chromatography steps.

4.1.1 Formulation, Packaging, and Labeling

SAR440894

SAR440894 is supplied as a lyophilized powder that is to be reconstituted with 2.3 mL sterile water for injection (SWFI). Upon reconstitution, a colorless to slightly brownish/yellowish and clear to slightly opalescent solution is obtained. The formulation is comprised of the following active pharmaceutical ingredient: 10 mM histidine, 8% sucrose, 0.02% polysorbate 80at a pH of 5.5. Extractable volume is 2 mL at 50 mg/mL (100 mg/vial).

Placebo

Placebo will be supplied as lyophilized 10 mM histidine, 8% sucrose, 0.02% polysorbate 80, pH of 5.5. Primary packaging is glass vials, to be reconstituted with 2.3 mL of SWFI (extractable volume 2 mL). The reconstituted product is clear and colorless.

SWFI, USP

The SWFI, USP is non-pyrogenic and contains no bacteriostatic, antimicrobial agent, or added buffer. This product should be used to reconstitute the SAR440894 product. Sterile WFI vials will be supplied as a single-dose container.

Each of these study products will be labeled according to manufacturer and regulatory specifications and include the statement “Caution: New Drug – Limited by Federal Law to Investigational Use.”

4.1.2 Product Storage and Stability

SAR440894

SAR440894 vials must be stored at 2 °C to 8 °C (36-46 °F) protected from light. Reconstitution should be performed at room temperature. Reconstituted product can be kept refrigerated (2 °C to 8 °C), if not immediately used (do not freeze). The reconstituted study product will be further diluted in IV bags containing normal saline. Once diluted, the study product should be stored at room temperature and protected from light prior to infusion. The total time from the start of the reconstitution to the start of the infusion should not exceed 4 hours.

Placebo

Vials containing lyophilized placebo must be stored between 2 °C to 8 °C.

SWFI, USP

Store at room temperature (20 °C to 25 °C or 68 °F to 77 °F [See USP Controlled Room Temperature]).

4.2 Acquisition/Distribution

SAR440894

SAR440894 for injection will be provided by Evotec and distributed through DMID CMS, Fisher BioServices.

Placebo

Placebo for injection will be provided by Evotec and distributed through DMID CMS, Fisher BioServices.

SWFI, USP

Sterile water for injection will be provided by the site.

Ancillary supplies

Ancillary supplies for IV administration, such as infusion sets and sodium chloride IV bags, will be provided by the site.

4.3 Dosage/Regimen, Preparation, Dispensing and Administration of Study Intervention/Investigational Product

See the protocol-specific MOP for detailed information on the preparation, labeling, storage, and administration of study product for each treatment. Study product preparation will be performed by the unblinded site research pharmacist on the same day as administration (Table 4-1) as outlined in the protocol-specific MOP. Prior to using any of the parenteral products, inspect for damage, contamination, discoloration, or particulate matter. Any product that fails inspection should be quarantined at 2-8°C and labeled as 'Do Not Use' (until further notice). The site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov and the DMID Clinical Project Manager for further instructions before any additional study product infusions. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product can be used. If it cannot be used, the site will receive specific instructions on how to return the affected study products to the DMID CMS or destroy it on site as outlined in the MOP.

Preparation of the product will be performed using aseptic techniques under a sterile environment (eg, biologic safety cabinet or laminar flow hood). Based on the subject weight on Day -1 and assigned cohort randomization, the appropriate weight-based dose will be calculated and the appropriate number of vials will be removed from storage to prepare the infusion. The placebo will be prepared in the same manner as the study product. The SAR440894 and placebo should be administered as a single IV infusion, using an infusion pump over 60 minutes. The IV administration set must contain a 0.2 µm in-line filter. Dose and volume calculations for study product and the placebo will be further described in the protocol-specific MOP.

The subjects will be admitted to the clinical site the day before the planned infusion (Day -1). Verification that the subject still meets all inclusion criteria and does not meet any exclusion criteria must be made prior to randomization. Administration procedures for the study product, including handling of infusion interruptions, are outlined in the MOP.

Table 4-1: Study Product Dosage and Regimen

Product Name	Dose	Route	Frequency of Administration	Duration of Infusion & Flush*
SAR440894	0.3, 1, 3, 10, or 20 mg/kg	IV infusion	Once	60 minutes
[Placebo]		IV infusion	Once	60 minutes
*The targeted infusion duration is 60 minutes, but has an acceptable range of 55 to 70 minutes.				

4.4 Predetermined Modification of Study Intervention/Investigational Product for an Individual Subject

Infusion interruptions (up to 1 hour) may be allowed for non-drug safety related issues (ie, IV infiltration or mechanical difficulties with the pump).

4.5 Accountability Procedures for the Study Intervention/Investigational Product(s)

Upon receipt of the study product, the site PI is responsible for the distribution and disposition of study product and has the ultimate responsibility for accountability. As this is a blinded study, the site PI will delegate this responsibility to the unblinded site research pharmacist. The unblinded site research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, temperature monitoring, storage conditions, and final disposition of the study product.

Used and unused investigational product vials will be stored at 2-8 °C in the investigational pharmacy until clinical trial accountability is completed and the sponsor approves of the disposition. Any used IV infusion bags and IV administration tubing should be disposed of as biohazardous waste per institutional requirements once administration is complete.

Upon completion of the trial or termination of the study and after the final monitoring visit, any remaining unused study drugs will either be returned or destroyed appropriately at the clinical

site in accordance with the disposition plan provided by the DMID CPM. Refer to the MOP for complete drug accountability and monitoring.

5 SELECTION OF SUBJECTS AND STUDY ENROLLMENT AND WITHDRAWAL

5.1 Eligibility Criteria

No exemptions are granted on subject inclusion/exclusion criteria in DMID-sponsored studies. Questions about eligibility should be directed toward the DMID medical officer.

5.1.1 Subject Inclusion Criteria

Subjects eligible to participate in this study must be in generally good health and meet all of the following inclusion criteria at Screening and Day -1:

1. Must be a healthy adult 18 to 45 years of age, inclusive, with a body mass index (BMI) greater than 18 or less than 35 kg/m^2, inclusive.
2. Participants of childbearing potential* having vaginal intercourse must use an effective method of contraception** from 45 days before study product administration through the final study visit.
   *Not sterilized via hysterectomy or bilateral oophorectomy and/or salpingectomy or be less than 1 year from the last menses if menopausal.
   **Includes any of the following (a) exclusive non-male sexual relationships; (b) monogamous relationship with vasectomized partner (≥ 180 days between procedure and subject receipt of investigational product); (c) bilateral tubal ligation or tubal occlusion (eg, Essure®); (d) effective intrauterine device (IUD); (e) hormonal implants (eg, Implanon®); (f) other hormonal contraceptives (such as birth control pills, vaginal rings, patches or injections); (g) barrier methods (condom, diaphragm, cervical cap) PLUS spermicide (gel or foam)
3. Women of childbearing potential must agree not to donate ova or oocytes (ie, human eggs) during the study.
4. Male subjects (including those with vasectomies) whose partners are of childbearing potential should use condoms with spermicide and not donate sperm for the duration of the study.
5. Must have adequate venous access for IV infusions and blood draws.
6. Agrees to be available for all study visits and willing to cooperate fully with the requirements* of the study protocol.

*Requirements include remaining in confinement for at least 72 hours after receiving study product and other activities outlined in the Schedule of Events.

7. Is able to understand the informed consent process and procedures and signs the consent form.
8. Will agree not to donate any blood or blood products* for the duration of the study.
   *Includes whole blood, red blood cells, platelets, plasma, or plasma derivatives.
9. Will agree to avoid travel to endemic areas (as defined by the CDC) for CHIKV at any point during the Follow-up period (https://www.cdc.gov/chikungunya/geo/index.html).

5.1.2 Subject Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria at Screening and Day -1:

1. Has any medical condition (eg, renal dysfunction) that, in the opinion of the site PI or appropriate sub-investigator listed on Form FDA 1572, is a contraindication to study participation.
2. Has any CS ECG abnormalities in the opinion of the site PI or appropriate sub-investigator been listed on Form FDA 1572.
3. Use of any prohibited prescription medication (excluding contraceptives in females) within 14 days before study product administration, through Day 56*.

   *Prohibited medications include immunosuppressives; immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); prescription Non-Steroidal Anti-inflammatory Drugs (NSAIDs); anti-neoplastic agents; any vaccine (licensed or investigational). If study activities overlap with the influenza season, subjects will be instructed to obtain influenza vaccine at least 45 days prior to proposed dosing or delay vaccination until after Day 56. Subjects will be instructed to obtain the last dose of any vaccine for SARS-CoV-2 (COVID-19) at least 45 days prior to proposed dosing or delay vaccination until after Day 56.
4. Use of nonprescription systemic drugs within 7 days before study product administration (includes vitamins, antacids*, over-the-counter drugs**, herbal/dietary supplements, etc.) through Day 28***.

   *Includes proton pump inhibitors and H2-blockers

   **Includes oral analgesics and anti-inflammatory drugs

   ***Nonprescription drugs and supplements may be allowed before Day 28 at the discretion of the site PI. In the event an OTC oral contraceptive becomes available during the course of the study, it must be reviewed and approved by the site PI.

5. Hypertension, with confirmed systolic blood pressure (BP) greater than 140 mm Hg or confirmed diastolic BP greater than 90 mm Hg, measured after 5 minutes of rest at Screening.
6. Hypotension, with confirmed systolic BP < 90 mm Hg.
7. Resting heart rate (HR) less than 45 bpm or greater than 100 bpm at Screening.
8. Body weight less than 50 kg.
9. History of a significant illness, per the investigators' clinical judgment, within 2 weeks before dosing (subjects can screen after illness is resolved for 2 weeks).
10. Known diagnosis of prolonged QT interval, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure.
11. Males with a mean QTcF greater than 450 msec or females with a mean QTcF greater than 470 msec (Fridericia's correction) at Screening.*

    *ECG tracings should be recorded at least 1 minute apart, after at least 5 minutes of rest in the supine position. If the mean QTcF value from the 3 tracings exceeds the limits stated, the subject is disqualified.
12. Any history of malignancy ever, except low-grade skin cancer (ie, basal cell carcinoma thought to be cured).
13. History of drug abuse, alcohol abuse, or significant psychiatric history according to the investigators' judgment within 12 months before Screening.
14. Positive for hepatitis B virus surface antigen, hepatitis C virus antibody, or human immunodeficiency virus (HIV) antibody at Screening.
15. Excessive consumption of beverages containing xanthine bases, or more than 400 mg of caffeine per day within 1 week of study product administration through the final study visit.
16. Consumption of alcohol within 24 hours before study product administration.
17. Use of nicotine-containing products within 45 days before study product administration through the final study visit.
18. Positive drug screen*, positive cotinine screen, or positive breathalyzer test for alcohol at Screening or admission (Day -1).

    *Cannabinoids, amphetamines, barbiturates, cocaine, opiates, benzodiazepines and phencyclidine. Subjects should be notified by phone not to consume any poppy seeds within 24 hours before the Screening urine test to avoid a false positive opioid test result.
19. If female, serum positive pregnancy test at Screening or serum positive pregnancy test on Day -1.
20. Breastfeeding throughout the duration of the study.

21. Total WBC and platelet counts, hemoglobin*, total bilirubin*, alanine/aspartate aminotransferase* and sodium* are Grade 1 or higher** at Screening visit***.

    *For sodium; potential subjects excluded prior to Protocol Version 6.0 with Grade 1 sodium values may be rescreened.

    For hemoglobin; a lower limit within 0.5 g/dL of the lower limit of normal (LLN) is allowable at Screening.

    For total bilirubin; ULN values will be allowed at Screening and Day -1/baseline provided the AST and ALT are within normal limits. Potential subjects excluded prior to Protocol Version 6.0 with bilirubin values below the Version 6.0 upper limit may be rescreened.

    For ALT/AST; subjects who screened prior to Protocol Version 11.0 were excluded if AST/ALT results were Grade 1 or higher at Screening. Subjects who screen with Protocol Version 11.0, AST/ALT is exclusionary if Screening results are 1.5 × ULN or if assessed as CS by the site PI.

    **Grade 1 or higher toxicity, see Appendix C and Appendix D for subjects who screened and enrolled prior to Protocol Version 11.0. Subjects who screen and enroll with Protocol Version 11.0, toxicity will be assessed with the NCI CTCAE, Version 5.0 – November 2017.4 Safety laboratory tests drawn on Day -1 or Screening if within 48 hours of planned dosing will serve as baseline values. Day -1 laboratory tests with a Grade 1 severity, other than those noted above, will not exclude subjects from participation.

    *** All other abnormal laboratory values collected at Screening and on Day -1 will be exclusionary at the discretion of the PI.

22. Potassium, bicarbonate, or creatinine/eGFR* results are Grade 1 or higher at either Screening or Day -1/Baseline visits.

    *For creatinine; subjects who screened prior to Protocol Version 11.0 were excluded if creatinine results were Grade 1 or higher. Subjects who screen with Protocol Version 11.0, creatinine is not an exclusionary criterion, instead subjects should have a calculated eGFR using Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (CKD-EPI) of ≥ 90 mL/min/1.73m^2 to be enrolled in the study.

23. Received an experimental agent (vaccine, drug, biologic, device, or medication) within 45 days or 5 half-lives (whichever is longer) before study product administration.*

    *Prior participation at any time in noninvasive methodology trials in which no drugs were given is acceptable.

24. Is participating in or plans to participate in another clinical trial with an interventional agent that will be received during this trial.
25. Has donated more than 500 mL of blood or blood products* within the month before Screening.

    *Includes whole blood, red blood cells, platelets, plasma, or plasma derivatives.
26. Has a history of serologically-proven CHIKV exposure at any point, or positive anti-CHIKV antibodies (ie, positive IgM or IgG) at Screening.
27. Has received blood products within 120 days prior to Screening.
28. Has received mAb in the past 3-months or 5 half-lives (whichever is longer) prior to Screening, whether licensed or investigational, or plans to receive a mAb outside of this study.

5.2 Withdrawal from the Study, Discontinuation of Study Product, or Study Termination

5.2.1 Withdrawal from the Study or Discontinuation of the Study Product

Subjects may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

An investigator may also withdraw a subject from receiving the study product for any reason. Follow-up safety evaluations will be conducted, if the subject agrees. If a subject withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms.

A subject may also be discontinued from participation in the study for any of the following reasons:

- Request by the subject to terminate participation in the study
- Inability to collect blood samples or receive study product due to poor venous access or other reasons
- Noncompliance, based on the opinion of the site PI
- Loss to Follow-up
- Request of primary care provider

- At the request of the IRB, DMID, or FDA
- Incarceration
- Subject's well-being, based on the opinion of the site PI
- SMC recommendation
- Death
- Additional information becomes available that makes further participation unsafe
- Subject withdraws informed consent
- Subject no longer meets eligibility criteria

5.2.2 Subject Replacement

Subjects who withdraw before receiving study product will be replaced. Up to 1 subject per cohort may withdraw after dosing but before Day 112 without being replaced. Should more than 1 subject from the same cohort withdraw from the study before Day 112, they will be replaced. Subjects who received any amount of study product will be encouraged to continue Follow-up (with subject's consent) for safety. Subjects withdrawing will be asked to complete the ET visit if they do not wish to be followed per protocol. Any decision to replace a subject who withdraws after receiving study product will be documented in a note to file. Replacement subjects will receive the same treatment as the subject being replaced. The Statistical and Data Coordinating Center (SDCC) must be contacted prior to enrolling any replacement subjects.

If a subject fails to appear for a safety Follow-up assessment, extensive effort (ie, 3 documented contact attempts via phone calls, email etc.,) made on separate occasions and followed by a certified letter) will be made to locate or recall him or her or at least to determine his or her health status. These efforts will be documented in the subject's records.

If an AE or SAE has occurred, every effort will be made to undertake protocol-specified safety Follow-up procedures, and the subject will be encouraged to receive appropriate medical care until the symptoms of the AE resolve or the subject's condition becomes stable. If a subject withdraws following dosing, analyses for safety, PK, and immunogenicity will be completed on blood samples already obtained.

5.2.3 Study Termination

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study subjects and assure appropriate therapy or follow-up for the subjects, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB.

6 STUDY PROCEDURES

6.1 Recruitment

Subjects will be recruited and enrolled in this study using IRB-approved procedures and materials, such as a subject-recruitment database, websites, outreach events, and electronic or other media. Recruitment, medical Screening, and study procedures will be performed separately at each site.

This study will not include special classes of subjects (eg, fetuses, neonates, prisoners, institutionalized individuals, or other vulnerable populations) for whom there are no known benefits in the Phase 1 trial.

Participation in this study will not routinely exclude women or minorities. Subjects will be recruited without regard to sex or race. Women of childbearing potential will be included but will undergo pregnancy testing and be required to use effective contraception from 45 days before study product administration until 150 days after study product administration (see inclusion criterion #2). Also, female subjects will be asked to contact the site PI if they become pregnant during the study. Male subjects will be asked to contact the site PI if their female partners become pregnant during the study (see inclusion criterion #4). Recruitment and Screening of alternate subjects is permitted to facilitate study enrollment. Alternative individuals will be allowed to enroll in the study if the original subjects do not participate for any reason. If the alternative is not selected on the dosing day, he or she will receive remuneration for their time and inconvenience and may return to participate in future cohorts if they are within the Screening window and meet eligibility. If alternative subjects are not dosed in the cohort when they originally met eligibility, they may be rescreened. No study procedures will be completed until signed informed consent has been obtained.

Subject inclusion and exclusion criteria must be assessed by a study clinician licensed to make medical diagnoses and listed on Form FDA 1572 as the site PI or sub-investigator.

6.2 Screening (Day -45 through Day -2) and Admission to Clinical Site (Day -1)

Each subject will undergo an eligibility screening. The following procedures will occur during Screening (Day -45 through Day -2):

- Obtain signed informed consent and Health Insurance Portability and Accountability Act authorization.
- Obtain a complete medical history, including assessment of concomitant medications, menstrual history (if applicable), and history of alcohol or drug abuse in the last 12 months.
- Record demographics.
- Record height and weight, calculate BMI using NIH calculator (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm). Screening weight will be used to determine participant eligibility and Day -1 weight will be used for dose calculations.
- Perform triplicate 12-lead ECGs with 10-second rhythm strips after subject has been supine for at least 5 minutes (before blood collections and within a 15-minute period, separated by at least 1 minute) and evaluate the rhythm to determine if any CS findings are present and confirm that the QTcF meets the inclusion criteria.
- Record vital signs (BP, heart rate, temperature, respiratory rate) after ECGs and before blood collections.
- Conduct complete physical examination.
- Collect blood samples for:
    - Hematology
    - Chemistry
    - Coagulation panel
    - Viral serology testing (CHIKV, HIV, hepatitis C virus, hepatitis B surface antigen)

  - Serum β-hCG pregnancy test for women of childbearing potential
  - Serum follicle-stimulating hormone only to confirm postmenopausal status
  - Estimated laboratory calculation of creatinine clearance and glomerular filtration rate.

- Collect a urine sample for:
  - Urinalysis dipstick
  - Urine with reflex microscopy if dipstick is positive for red blood cells, white blood cells, or protein. Urinalysis will be repeated as described in the footnote section of Table 7-1 for menstruating females.
  - Urine drug screen including cotinine. Subjects should be notified by phone not to consume any poppy seeds within 24 hours before the screening urine test to avoid a false positive opioid test result.
- Breathalyzer to test for presence of alcohol.
- Record all prior/concomitant medications taken with in previous 45 days of Screening.
- Review childbearing potential and contraception (if applicable).
- Council on the avoidance of pregnancy.

All subjects will be informed of their eligibility and, if selected, will be asked to avoid extreme physical activity (for example: long distance running or biking, weight lifting, or playing contact sports) from Screening until discharge from the clinical site on Day 4.

All laboratory testing for screening and safety monitoring will be performed at the clinical site's clinical laboratory improvement amendments (CLIA) approved laboratories indicated on the Form FDA 1572.

A repeat of exclusionary safety assessments (ie, vital sign measurements, ECGs, and clinical laboratory assessments) is permitted at Screening and on Day -1 at the discretion of the PI.

All subjects will arrive at the clinical site no later than the day before study product administration (Day -1). If screening laboratory tests occurred within 48 hours of admission, they do not have to be repeated except for the pregnancy test for females of childbearing potential and the breathalyzer and urine drug screen for all subjects. If a subject meets eligibility criteria but

was not dosed, the subject can be reevaluated (rescreened) once for participation in the study. If a subject is reevaluated (rescreened) within 3 months of serological testing (CHIKV, HIV, hepatitis C virus, hepatitis B surface antigen), it will not be repeated. The subject's history must be reviewed to ensure no new risk factors for hepatitis or HIV have occurred since the last serological testing.

For detailed instructions of each assessment and procedure, refer to the Schedule of Events in Appendix A.

The following procedures will occur upon admission to the clinical site (Day -1):

- Confirm that the subject meets all study inclusion criteria and no exclusion criteria.
- Obtain weight for dose calculations.
- Obtain an interim medical history since Screening.
- Confirm concomitant medication usage and review of birth control since Screening.
- Admit subject.
- Record vital signs before blood collections.
- Conduct complete physical examination.
- Collect blood specimen for:
    - Hematology
    - Chemistry
    - Coagulation panel
    - Serum β-hCG pregnancy test for women of childbearing potential
    - Renal injury biomarker serum cystatin-C.
- Collect a urine specimen for:
    - Urinalysis dipstick
    - Urine with reflex microscopy if dipstick is positive for red blood cells, white blood cells, or protein (see Table 7-1 for a complete list of clinical laboratory

evaluations). Urinalysis will be repeated as described in the footnote section of Table 7-1 for menstruating females.

- Urine drug screen
- Cotinine screen.

- Perform breathalyzer test for presence of alcohol.
- Randomization

6.3 Confinement and Infusion (Day 1 through Day 4)

For detailed instructions of each assessment and procedure, refer to the Schedule of Events in Appendix A.

The following procedures will occur prior to dosing on the day of study product administration (Day 1):

- Review medical history.
- IV catheter insertion for administration of study product. Straight stick or IV catheter insertion for collection of blood samples. If catheters are utilized, they will be placed in different arms.
- Perform triplicate 12-lead ECGs with 10-second rhythm strips after subject has been supine for at least 5 minutes (before blood collections and within a 60-minute period prior to dosing, separated by at least 1 minute). The ECG will be obtained within a 60-minute period prior to dosing and within approximately 15 minutes after dosing is complete. Continuous remote telemetry monitoring will be conducted from 30 minutes prior to study product administration to approximately 4 hours post dose.
- Record vital signs before blood collections. Vital signs will be checked within a 60-minute period prior to dosing and approximately every 15 minutes during the infusion.
- Record concomitant medications and review of birth control.
- Conduct symptom-directed physical examination as needed.
- Obtain blood for PK and immunogenicity (ie, ADA) analyses (see Section 7.2.2.1).

- Collect blood specimen for:
    - Hypersensitivity panel.

The following procedures will occur during product administration:

- Administer study drug product.
- Collect vital signs every 15 minutes (±5 minutes) during the infusion.
- Direct observation by RN or designated clinical staff for the duration of the infusion.
- Symptom-directed physical examination for AE or SAE, signs and symptoms of infusion reaction, or at the discretion of the investigator
    - Collect blood specimens for hypersensitivity panels if infusion reaction occurs. Should an anaphylactic or anaphylactoid-type reaction occur, the subject will be treated using the standard protocol at the clinical site. Infusion-related AEs and suspected hypersensitivity reactions will be documented including clinical presentation and severity (based on grading scales in Appendix B and NCI CTCAE, Version 5.0 – November 2017) of the event.
    - Symptom-directed treatment at direction of qualified investigator or sub-investigator.

The following procedures will occur following product administration (end of infusion):

- Obtain blood for PK analysis (see Section 7.2.2).
- After the infusion, vital signs will be taken at the following time points: 1, 2, 4, and 6 hours with an acceptable window of ±5 minutes for each time point.
- Symptom-directed physical examination for AE, signs and symptoms of infusion reaction, or at the discretion of the investigator.

The following procedures will occur on the days following study product administration (Day 2 and Day 3):

- Record vital signs before blood collections.
- Conduct symptom -directed physical examination as needed.

- Collect blood specimen each day for:
    - Hematology
    - Chemistry
    - Coagulation panel
    - Renal injury biomarker serum cystatin-C.
- Collect a urine specimen each day for:
    - Urinalysis dipstick
    - Urine with reflex microscopy if dipstick is positive for red blood cells, white blood cells, or protein (see Table 7-1 for a complete list of clinical laboratory evaluations). Urinalysis will be repeated as described in the footnote section of Table 7-1 for menstruating females.
- Assess, identify, and record any AEs or SAEs after first dose of study product.
- Record concomitant medications.
- Obtain blood for PK analysis (see Section 7.2.2.1).

The following procedures will occur on the day of discharge from the clinical site (Day 4):

- Perform triplicate 12-lead ECG with 10-second rhythm strips after subject has been supine for at least 5 minutes (before blood collections and within a 15-minute period, separated by at least 1 minute).
- Record vital signs before blood collections.
- Conduct complete physical examination.
- Collect blood specimen for:
    - Hematology
    - Chemistry
    - Coagulation panel
    - Renal injury biomarker serum cystatin-C.

- Collect a urine specimen for:
    - Urinalysis dipstick
    - Urine with reflex microscopy if dipstick is positive for red blood cells, white blood cells, or protein (see Table 7-1 for a complete list of clinical laboratory evaluations). Urinalysis will be repeated as described in the footnote section of Table 7-1 for menstruating females.
- Review laboratory data (including all Day 4 safety labs with the exception of cystatin-C), vital signs, and assess, identify, and record any AEs or SAEs after study product administration.
- Record concomitant medications and review of birth control.
- Council on the avoidance of vaccines (with exception of influenza and COVID-19 vaccines after Day 56 per Section 5.1.2).
- Obtain blood for PK analysis (see Section 7.2.2.1).
- Counsel on the avoidance of pregnancy (all participants) and prohibited medications/substances, including lifestyle restrictions (eg, no tobacco use or vaping, no excessive caffeine intake [> 400 mg of caffeine per day], and to avoid extreme physical activity 72 hours prior to Follow-up visits).
- Discharge from the clinical site following review of safety labs, ECG, and other assessments and counsel on reporting changes in well-being between visits.

6.4 Outpatient Study Visits

6.4.1 Follow-up (Day 7 ±1, 14 ±2, 28 ±4, 56 ±4, 84 ±7, 112 ±7)

- Confirm concomitant medication usage and review of birth control since last visit.
- Record vital signs before blood collections.
- Conduct symptom-directed physical examination as needed.

- Collect blood specimen for:
    - Hematology
    - Chemistry
    - Coagulation panel
    - Renal injury biomarker serum cystatin-C.
- Collect a urine specimen for:
    - Urine β-hCG pregnancy test for all women of childbearing potential (see Schedule of Events in Appendix A for timing)
    - Urinalysis dipstick
    - Urine with reflex microscopy if dipstick is positive for red blood cells, white blood cells, or protein (see Table 7-1 for a complete list of clinical laboratory evaluations). Urinalysis will be repeated as described in the footnote section of Table 7-1 for menstruating females.
- Obtain blood for PK and immunogenicity analyses (see Section 7.2.2.1).
- Assess, identify, and record any AEs or SAEs after the administration of study product.
- Counsel on the avoidance of pregnancy (males and females) and prohibited medications/substances, including lifestyle restrictions (eg, no tobacco use or vaping, no excessive caffeine intake [> 400 mg/day], and to avoid extreme physical activity 72 hours prior to Follow-up visits).
- Counsel on the avoidance of vaccines at Follow-up visits through Day 56.

6.4.2 Final Study Visit (Day 150 ±7)

- Confirm concomitant medication usage and review of birth control since last visit.
- Record vital signs before blood collections.
- Conduct complete physical examination.

- Perform triplicate 12-lead ECGs with 10-second rhythm strips after subject has been supine for at least 5 minutes (before blood collections and within a 15-minute period, separated by at least 1 minute).
- Collect blood specimen for:
    - Hematology
    - Chemistry
    - Coagulation panel
    - Renal injury biomarker serum cystatin-C.
- Collect a urine specimen for:
    - Urinalysis dipstick
    - Urine β-hCG pregnancy test for all women of childbearing potential
    - Urine with reflex microscopy if dipstick is positive for red blood cells, white blood cells, or protein (see Table 7-1 for a complete list of clinical laboratory evaluations). Urinalysis will be repeated as described in the footnote section of Table 7-1 for menstruating females.
- Obtain blood for PK analyses and immunogenicity (see Section 7.2.2.1).
- Assess, identify, and record any AEs or SAEs after the administration of study product.

6.4.3 Early Termination Visit (if needed)

- Confirm concomitant medication usage and review of birth control since last visit.
- Record vital signs before blood collections.
- Conduct complete physical examination.
- Perform triplicate 12-lead ECGs with 10-second rhythm strips after subject has been supine for at least 5 minutes (before blood collections and within a 15-minute period, separated by at least 1 minute).

- Collect blood specimen for:
    - Hematology
    - Chemistry
    - Coagulation panel
    - Renal injury biomarker serum cystatin-C
    - Hypersensitivity panel (if suspected infusion reaction).
- Collect a urine specimen for:
    - Urinalysis dipstick
    - Urine β-hCG pregnancy test for all women of childbearing potential
    - Urine with reflex microscopy if dipstick is positive for red blood cells, white blood cells, or protein (see Table 7-1 for a complete list of clinical laboratory evaluations). Urinalysis will be repeated as described in the footnote section of Table 7-1 for menstruating females.
- Obtain blood for PK and immunogenicity analyses (see Section 7.2.2.1).
- Assess, identify, and record any AEs or SAEs after the administration of study product.
- Counsel on the avoidance of pregnancy (males and females) and prohibited medications/substances until 150 days has elapsed from receipt of study product.
- If subject is unwilling or unable to have an in person ET visit, study team will attempt to contact subject via telephone to review medical history, concomitant medications, and AEs.

6.5 Unscheduled Study Visits

A subject may return to the clinical site for an unscheduled visit at any time for specimen collection, AE Follow-up, re-screening, or at the discretion of the PI. The following procedures

will be performed at the discretion of the PI. Additional procedures may be performed, as needed, at the discretion of the PI.

- Record vital signs before blood collection.
- Conduct a symptom-directed physical exam.
- Assess, identify, and record any AEs or SAEs after the administration of study product.
- Record all prior/concomitant medications and review of birth control.
- Obtain an interim medical history.

6.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the site PI, or the site personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with International Council for Harmonisation (ICH) E6:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1, and 5.20.2

It is the responsibility of the site PI and other study personnel to use continuous vigilance to identify and report deviations. All deviations must be promptly reported to DMID per the SDCC protocol deviation reporting procedures.

All protocol deviations, as defined above, must be addressed in study subject data collection forms. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart. Protocol deviations must be sent to the IRB/IEC of record per their guidelines. The site PI and other study personnel are responsible for knowing and adhering to IRB requirements.

7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

The Schedule of Events is presented in Appendix A. For timing of and instructions for performing the laboratory assessments, see the Schedule of Events and the Laboratory Manual; for a list of specific laboratory tests to be performed, see Table 7-1.

7.1 Clinical Evaluations

The following clinical evaluations will be completed during the study:

- Complete medical history: includes current diagnoses, past diagnoses, surgical history, current medications, date of last menses for women, current contraceptive methods, smoking status, and allergies.
- Interim medical history: includes medical history that occurred between previous encounter and current visit.
- Concomitant medications: includes current medications, medications in the past 45 days prior to dosing (including OTC, herbals, vaccines, prescription, supplements, vitamins and illicit substances).
- Height at screening. Weight and BMI at screening and Day -1. Screening weight will be used to determine participant eligibility and Day -1 weight will be used for dose calculations.
- Vital signs: temperature, heart rate, BP, and respiratory rate within normal limits will be assessed once at each time point per the Schedule of Events. Subjects will rest supine for at least 5 minutes prior to vital signs measurement. If a physiologic parameter, eg, a vital sign, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the site PI, the abnormality is the result of an acute, short-term, rapidly reversible condition (eg, stress, anxiety, or “white coat syndrome”). A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by a malfunctioning or inappropriate measuring device (eg, inappropriately sized BP cuff).

- Once study product administration has started, any AEs involving BP and HR, 3 measurements on the same arm used for previous vital sign measurements at least 5 minutes apart with concordant results will be taken to confirm.
- Complete physical examination*: general appearance, head, ears, external examination of eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes.
- Symptom-directed physical examination* (performed only if a participant endorses a symptom and at the discretion of the PI). The symptom-directed physical exam will be limited to one or more of the body systems as described under "complete physical examination", localized to the participant's complaint(s) at the discretion of the examining provider.

  *All physical examinations will be performed by qualified investigator or sub-investigator listed on the Form FDA 1572.
- 12-lead ECG: subjects will be asked to rest supine for at least 5 minutes prior to ECG.
    - Triplicate ECGs with 10-second rhythm strips will be obtained within a 60-minute period prior to dosing and within approximately 15 minutes after dosing is complete, separated by at least 1 minute.
    - Single, standard 12-lead safety ECGs will also be obtained.
    - All ECG recordings will be taken before obtaining any blood sample.
    - Significant changes are defined as the following:
        - Any significant change in rate or rhythm as determined by the site PI
        - QTcF interval of greater than 450 msec (male) or greater than 470 msec (female)
        - Increase from the QTcF baseline (defined as mean of pre-dose measurements) greater than 50 msec until the change resolves.

      If any of these changes are observed, triplicate ECG tracings, approximately 2 minutes apart, should be recorded and repeated hourly until cessation of the abnormality.

- Reader will sign and date the safety ECGs and provide a global interpretation using the following categories:
  - Normal
  - Abnormal—not clinically significant (NCS)
  - Abnormal—CS
- Clinically significant ECG findings with new onset (or change in severity or frequency) any time after the administration of study product will be recorded as AEs. Clinical significance of ECG findings will be determined by the site PI based on his/her overall interpretation of data. Original ECG tracings will be retained as source documentation in the subject's records at the clinical site.
- During the study, from 30 minutes before the administration of study product until approximately 4 hours post dose, continuous 12-lead ECG remote telemetry monitoring will be conducted to assess for acute changes. If a CS change occurs, the monitoring will be continued until it has resolved and it is deemed safe to discontinue monitoring by the site PI or designee.

7.1.1 Assessment of Concomitant Medications/Treatments Other Than Study Product

All OTC medications or herbal, nutritional, and dietary supplements within 7 days and selected prescription medications within 14 days before study product administration are prohibited per exclusion criteria. Influenza vaccine and COVID-19 vaccine are permitted if given more than 45 days before study product administration or after Day 56. No other vaccines are permitted within 45 days of study product administration or duration of study. Concurrent therapy with any prescription or OTC medication (except for acetaminophen or NSAID in the case of necessary treatment of AEs) during the course of the protocol after randomization should be reviewed by the site PI before study product infusion, unless appropriate medical care necessitates that therapy should begin before the site PI can be consulted. Nonprescription systemic drugs may be used after Day 28 while prescription drugs (excluding contraceptives in females) may be used after Day 56.

Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications will include all current medications and medications taken in the 45 days before study treatment administration through the last study visit.

7.1.2 Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device

Subjects will be directly observed at the time of dosing by a blinded member of the clinical research team who is trained and delegated to administer the study product. Treatment compliance will be documented in the electronic case report form (eCRF) by recording the date, start time, stop time, and whether the dose of study product was completely infused.

7.2 Laboratory Evaluations

Refer to Table 7-1 for a complete list of clinical laboratory evaluations and to the Schedule of Events (Appendix A) for corresponding time points.

7.2.1 Clinical Laboratory Evaluations

Laboratory reference ranges for the site that screened and enrolled subjects prior to Protocol Version 11.0 are provided in Appendix C and Appendix D. Laboratory reference ranges for sites that screen and enroll subjects with Protocol Version 11.0 are provided in the MOP. Each site will maintain a list of the normal ranges and units of measurement for the laboratory parameters to be determined during this study, and the data and certification number of the laboratory. If the normal ranges change during the course of the study, the site investigator must update this list with the new ranges and effective dates. The normal laboratory reference ranges will also be retained in the regulatory binder at each site.

Table 7-1: Clinical Laboratory Evaluations

Hematology	Chemistry	Urinalysis
Hemoglobin^{+}	Alanine aminotransferase^{++}	Protein
Platelet count*	Aspartate aminotransferase^{++}	Blood^
White blood cell count*	Creatinine***	Ketones
Hematocrit	Bilirubin, total*	Glucose
Red blood cell count	Sodium**	Bilirubin
Basophil count	Potassium**	Nitrites
Eosinophil count	Bicarbonate**	Urobilinogen
Lymphocyte count	Glucose (random at Screening, otherwise fasting for a minimum of 2 hours)	White blood cells
Monocyte count		Protein-to-creatinine ratio^^
Neutrophil count	Blood urea nitrogen	**Note:** If any abnormal value is observed on the urine dipstick test,

Table 7-1: Clinical Laboratory Evaluations

Hematology	Chemistry	Urinalysis
	Pregnancy test (serum or urine) Calcium Alkaline phosphatase Bilirubin, direct Albumin Protein, total Estimated glomerular filtration rate*** Follicle stimulating hormone Cystatin-C Creatinine Clearance	the sample should be further analyzed with urine chemistry and microscopy.^^^ Urinalysis will be repeated as necessary for menstruating females.
Coagulation	**Drugs of Abuse (Urine) and Alcohol Testing****	**Serology Screen**
Activated partial thromboplastin time Prothrombin time International normalized ratio	Cannabinoids Amphetamines Barbiturates Cocaine Opiates including Methadone Benzodiazepines Phencyclidine Cotinine Breathalyzer (alcohol)	Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus 1 and 2 antibody with antigen CHIKV IgG and IgM antibody

Any lab value may be repeated if felt erroneous due to laboratory error.

*Values outside the acceptable limits at Screening only are exclusionary with exception of total bilirubin for which ULN values will be allowed at Screening and Day -1/Baseline provided the AST and ALT are within normal limits.

**Values outside the acceptable limits at Screening and Day -1 are exclusionary.

***Values for creatinine results that Grade 1 or higher at Screening and Day -1 prior to Protocol Version 11.0 were exclusionary. With Protocol Version 11.0, creatinine is not an exclusionary criterion, instead subjects should have a calculated eGFR using the CKD-EPI of ≥ 90 mL/min/1.73m^2 to be enrolled in the study.

$^+$For hemoglobin; a lower limit within 0.5 g/dL of the LLN is allowable at Screening.

$^{++}$For AST/ALT; results are exclusionary if Screening results are 1.5 × ULN or if assessed as CS by the site PI.

^Urine abnormalities in menstruating females will trigger repeat urinalysis within the next 14 days, either at a scheduled study visit or via unscheduled study visit following cessation of menses. Urine abnormalities in females attributable to menstruation will not be considered AEs.

^^Urine protein-to-creatinine ratio will be calculated at Screening and Day -1.

^^^Repeat urine collection if cellular elements in the microscopic exam indicate the participant did not successfully follow clean catch instructions.

7.2.2 Research Assays

- SAR440894 plasma concentrations will be determined by using a validated enzyme-linked immunosorbent assay.
- ADA in K3EDTA plasma will be assessed by using validated bridging electrochemiluminescence assays for Screening, confirmation and titration.
- Plasma PK samples should be collected in tubes that contain K3EDTA anticoagulant using venipuncture. For PK blood samples collected on Day 1, the arm other than used for drug infusion will be used.
    - For blood sample collection, there will be an acceptable window of ±10 minutes in the first 8 hours after dosing and ±30 minutes between 9 and 72 hours. PK samples at Follow-up visits will be collected during the designated Follow-up window. The "end of infusion" sample should be obtained within 5 minutes of the end of the infusion. Actual times of blood sample acquisition will be carefully recorded.
    - PK samples collections will be performed at the following time points: Baseline pre-infusion (60 to 0 minutes prior to start of infusion), at the completion of the infusion, and at (relative to the end of the infusion): 1, 4, 8, 12, 24, 48, and 72 hours, and on Day 7 ±1, Day 14 ±2, Day 28 ±4, Day 56±4, Day 84±7, Day 112±7, Day 150 ±7, and ET (if needed).
    - PK samples will be analyzed by Aptuit (Verona) Srl.
- Immunogenicity samples for ADAs will be analyzed by Aptuit (Verona) Srl.
    - Plasma samples for ADA measurements will be collected pre-infusion (60 to 0 minutes prior to start of infusion), Day 56 ±4, Day 112 ±7, Day 150 ±7, and ET.

7.2.2.1 Blood Volume

The total amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 450 mL.

7.2.2.2 Laboratory Specimen Preparation, Handling, and Storage

Instructions related to handling of safety laboratory samples and PK blood samples, including how to process blood and prepare aliquots, sample storage, and disposition are provided in the MOP.

A hypersensitivity sample will be collected on all subjects at baseline (pre-dose on Day 1) and stored frozen on site. If a subject experiences anaphylaxis or an anaphylactoid event related to the infusion, three additional samples will be collected during onset, 2 or more hours after onset and after resolution of symptoms. Samples will only be analyzed in the event of a hypersensitivity reaction. Hypersensitivity samples will be collected, processed and stored frozen on site and sent to the testing lab if needed. Baseline samples will be discarded at the end of the study if there are no hypersensitivity events. Prior to discarding samples, DMID or an authorized representative must notify the site and approve sample destruction.

Details on the collection, storage, testing, and disposition of used and unused hypersensitivity samples will be provided in the protocol-specific MOP.

7.2.2.3 Laboratory Specimen Shipping

Specimen shipment will occur at intervals during this study following all applicable International Air Transport Association requirements and according to the specifics for storage temperature and documentation as detailed in the central (clinical) laboratory manual and MOP as appropriate.

Further instructions for specimen shipment are included in the MOP, as appropriate.

Clinical laboratory assessments will be performed by the clinical site CLIA approved laboratories indicated on the Form FDA 1572. Plasma samples for PK analyses and ADA will be shipped on dry ice to Fisher BioServices before sending them to Aptuit (Verona) Srl.

Fisher BioServices
20439 Seneca Meadows Parkway
Germantown, MD 20876
Telephone: 240-477-1350

Email: DMID.CMS@ThermoFisher.com
Fax: 240-477-1360

8 ASSESSMENT OF SAFETY

8.1 Assessing and Recording Safety Parameters

Safety will be assessed through the evaluation of AEs, vital signs, ECGs, and conventional clinical laboratory data (clinical chemistry panels and hematology, coagulation, immunogenicity, and urinalysis evaluations), according to the Schedule of Events (Appendix A).

8.1.1 Adverse Events

International Council for Harmonisation E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. The FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A treatment-emergent AE (TEAE) is defined as an AE that occurs during or after the first study product infusion and up through the final visit. Only TEAEs will be documented as AEs in this study. Adverse events that occur between the time of consent and administration of study product will be recorded in the medical history.

An AE can therefore be any unfavorable and unintended sign (including a CS abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs will be captured on the appropriate data collection form and eCRF. Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator), date of resolution, seriousness, and outcome. Adverse events occurring during the study collection and reporting period will be documented appropriately regardless of relationship. Adverse events will be followed through resolution or stabilization, as indicated by an investigator.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

Medically-indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local site laboratory.

The site investigator should employ the best medical judgment in determining how to manage AEs and SAEs.

8.1.1.1 Adverse Events Grading

All AEs (laboratory and clinical symptoms) will be graded by the licensed study physicians on Form FDA 1572 for severity and assessed for relationship to study product. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF.

Severity of Event:

Subjects who screened and enrolled prior to Protocol Version 11.0, AEs will be assessed by the investigator using a protocol-defined grading system (see Toxicity Table, Appendix B). For events not included in the protocol-defined grading system, the following guidelines will be used to determine severity:

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affect clinical status, may require intensive therapeutic intervention, or death related to an AE. Severe events are usually incapacitating.

Subjects who screen and enroll with Protocol Version 11.0, AEs will be assessed by the investigator using the NCI CTCAE, Version 5.0 – November 2017.[4] For events not included in the NCI CTCAE grading system, the following guidelines will be used to determine severity:

- Grade 1 (Mild): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2 (Moderate): Minimal, local, or noninvasive intervention indicated; limits age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- Grade 3 (Severe): Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limits self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 (Life threatening): Urgent intervention indicated.
- Grade 5 (Death).

Relationship to Study Product: The assessment of the AE's relationship to study product will be done by the licensed study physician indicated on the Form FDA 1572 and the assessment will be part of the documentation process. Whether the AE is related or not is not a factor in determining what is or is not reported in this study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical study, the study product must always be suspect. The relationship to study product will be assessed for AEs using the terms "Related" and "Not Related".

- An investigator should use good clinical judgment. If the event is believed to be unrelated to study product, an alternative plausible explanation must be provided. Otherwise, AEs will be considered related to the study product.

8.1.2 Serious Adverse Events

An AE or suspected adverse reaction is considered an SAE if it occurs between the time of receiving study medication and the final study visit, and in the view of either the site PI or sponsor; it results in any of the following outcomes:

- Death,
- A life-threatening* AE,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical 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.

*Life-threatening AE: An AE is considered "life-threatening" if, in the view of either the site PI or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 or by the Institution as the site PI or sub-investigator.
- Recorded on the appropriate SAE data collection form and eCRF.
- Followed through resolution by a licensed study physician (for IND studies, a physician listed on the Form FDA 1572 as the site PI or sub-investigator).
- Reviewed and evaluated by DMID or SMC (periodic review unless related), and the IRB/IEC.

8.1.3. Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the IB, Package Insert, and/or Summary of Product Characteristics.

The IND Sponsor is responsible for making the determination of which SAEs are "serious and unexpected suspected adverse reactions" (SUSARs) as defined in 21 CFR 312.32.

- *Suspected Adverse Reaction* means any AE for which there is a reasonable possibility that the drug caused the AE.
- *Unexpected Adverse Event* means an AE that is not listed at the specificity or severity that has been observed.

All SUSARs (as determined by the IND Sponsor) will be reported to the FDA as IND Safety Reports per 21 CFR 312.32 as soon as possible but not exceeding 7 calendar days for unexpected fatal or life-threatening events, and not exceeding 15 calendar days for other qualifying events. IND Safety Reports will also be provided to the IRB.

8.1.4 Unanticipated Problem

An Unanticipated Problem (UP) is defined as any incident, experience, or outcome that meets all the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; and
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects, or others (which may include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or expected.
- A UP must be reported within 7 calendar days of an investigator becoming aware of the actual or suspected UP.

8.2 Specification of Safety Parameters

Safety will be assessed by the frequency and severity of AEs and SAEs; the incidence and maximum intensity of AEs and SAEs, vital sign measurements, ECG findings, and clinically important changes in clinical laboratory values, defined as a change to a higher grade relative to baseline.

AEs and SAEs will be addressed as they are reported or identified by a staff member. Safety laboratory reports are reviewed as available, generally within 24 hours of sample collection.

8.2.1 Solicited Events

Solicited events are AEs that are common and known to occur following administration of study product. There are no solicited events for this study.

8.2.2 Unsolicited Events

Unsolicited events are any other AEs that occur following infusion of study product.

8.3 Reporting Procedures

8.3.1 Reporting Serious Adverse Events

Serious AEs will be followed until resolution even if this extends beyond the study reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on a DMID SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group

Clinical Research Operations and Management Support (CROMS)

6500 Rock Spring Dr. Suite 650

Bethesda, MD 20817, USA

SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)

SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)

SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, select SAE data fields must also be entered into the SDCC system. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The site will send a copy of the SAE report(s) when they are provided to the DMID Pharmacovigilance Group. The DMID Medical Monitor and DMID Clinical Project Manager

will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

An Independent Safety Monitor (ISM) is not required for this study.

8.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the site PI or appropriate sub-investigator, DMID, as the IND Sponsor, will report any suspected unexpected SAE. DMID will report an AE as a suspected unexpected AE only if there is evidence to suggest a causal relationship between the study intervention and the AE. DMID will submit an IND safety report to the FDA and will notify all participating site PIs (ie, all PIs to whom the sponsor is providing drug under its IND[s] or under any PI's IND[s] of potential serious risks from clinical studies or any other source, as soon as possible). DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Upon request from the FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All SAEs designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

8.3.3 Reporting of Pregnancy

Females of childbearing potential are excluded from this study unless they consent to adequate contraception.

Female subjects, and female partners of male subjects, must be instructed to inform the investigator immediately if they become pregnant during the study. In the event of a confirmed pregnancy or positive pregnancy test, the following actions should be taken:

- Pregnancy should be reported to Emmes within 24 hours of notification, using the applicable pregnancy report form.
- Investigator should counsel the subject regarding the possible effects of prior SAR440894 exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.
- Subject should be followed, if possible, until the immediate postnatal period (6 weeks) or until termination or loss of the pregnancy. The outcome should be reported to the Medical Monitor using the Pregnancy Outcome or Abnormal Pregnancy Outcome form.

Pregnancy is not an AE itself. However, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered an SAE and will be reported as described in the AE and SAE sections. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the sponsor/DMID.

8.4 Type and Duration of Follow-up of Subjects After Adverse Events

AEs and SAEs will be followed through resolution or stabilization, as indicated by an investigator.

Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

8.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

The site principal investigator or sub-investigator is responsible for recording all AE/SAEs that are observed or reported during this trial, regardless of the relationship to study product. AE/SAEs, abnormal CS laboratory test values, or abnormal clinical findings will be collected, assessed, documented, and followed appropriately. Subjects who screened and enrolled prior to Protocol Version 11.0, grading of the ECG AEs will be based on the Appendix B toxicity table

and grading of the laboratory and vital signs AEs will be based on the Appendix C and Appendix D. Subjects who screen and enroll with Protocol Version 11.0, toxicity will be assessed with the NCI CTCAE, Version 5.0 – November 2017.4

Isolated laboratory test abnormalities should not be recorded as AEs or SAEs; eg, if the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, CS laboratory abnormalities or other abnormal test assessments (eg, ECGs) that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE) as described in Section 8.1. Clinically significant laboratory test abnormalities are documented on the laboratory form and not recorded as a separate AE eCRF but the relationship, clinical significance and grade are noted on the laboratory screen.

The site is utilizing standard panels for this protocol therefore if there are laboratory parameters not solicited in this protocol but are part of a standard panel that are abnormal and CS as determined by the site PI then the abnormal parameter will be reported on the AE eCRF.

8.6 Halting Rules

The stopping rules outlined below will be used to evaluate whether it is safe to proceed with dose escalation or whether the study should be suspended for further safety evaluation. If any halting criteria are met, enrollment and dosing for subjects will be suspended at all sites until the event is assessed by the SMC.

The SRC may be convened to provide an option for a rapid review of available safety data collected following the sentinel subjects in each group. Otherwise, confirmation by the site PI that the sentinel subjects did not meet any of the predefined objective criteria and approval by the DMID MM will suffice for expansion of enrollment in the rest of the subjects in each cohort. If any of the halting rules below are met, further dosing will be halted pending SMC review.

At predefined time points (Section 8.7), the SRC will meet to review all safety data for the cohort in question to determine if the escalation-halting rules have been met. In addition, the SDCC will provide study team with documentation of whether halting rules were/were not met after all the relevant safety data has been entered into the electronic data capture system up to Day 14 for subjects in the cohort. If none of the rules has been met through Day 14 into each cohort, the DMID MM will give approval for the next cohort to begin enrollment. If a

dose-escalation halting rule is met, the SMC will need to convene to recommend to DMID the next steps.

Dose-escalation decisions will be documented by the DMID MM. This documentation will include whether halting criteria were met and, if applicable, any review and actions of the SMC.

8.6.1 Sentinel Subject Halting Rules

The site PI will review sentinel subject data from dosing through Day 4 to confirm that sentinel subject(s) data have not met predefined halting criteria and notify the DMID Medical Monitor prior to proceeding with dosing the remaining cohort.

- Any SAE, regardless of the relationship to the study product (with the exception of death or hospitalization that was the result of trauma or accident).

  OR

- A sentinel subject within a cohort experiences a **related** Grade 3 or higher AE (laboratory or systemic) not resolved within 24 hours through Day 4. Resolution is defined as down to Grade 1 or Baseline. Note: If the event starts on Day 4, the review period will be extended to Day 5

If the predefined criteria for sentinel subject are met, the SMC will review the study data and provide guidance on how to proceed.

8.6.2 Cohort Dose-Escalation Halting Rules (Dosing through Day 14)

- One subject has an SAE that is determined to be **related** to the study product.

  OR

- Two or more subjects in a cohort experience Grade 2 or higher **related** AE (laboratory or systemic) that is coded in the same high level group term (HLGT) per MedDRA classification.

If the predefined criteria for dose escalation halting are met, the SMC will review the study data and provide guidance on how to proceed.

8.6.3 Study Halting Criteria

- One subject has an SAE that is determined to be **related** to study product.

  OR

- Three or more subjects in the study (cumulative among all cohorts) experience a Grade 3 **related** AE (laboratory or systemic) that is coded in the same HLGT per MedDRA classification.

8.6.4 Infusion Halting Rules

Infusion of the Investigational Product will be halted if any of the following manifestations of anaphylaxis develop and will not be restarted. Symptoms of anaphylaxis may begin in seconds or minutes of infusion.

- Skin or mucous membrane manifestations: hives, moderate or severe pruritus, or angioedema (usually of face, eyelids, or lips, tongue or uvula).
- Respiratory compromise: sensation of throat closure or choking, chest tightness, wheezing, stridor.
- A decrease in systolic BP to < 90 mmHg or > 30% decrease from baseline in systolic or diastolic BP.
- Tachycardia with an increase in resting heart rate to ≥ 130 beats per minute (bpm); or development of a ventricular dysrhythmia; or bradycardia < 45 bpm (or < 40 bpm in subjects with a baseline of < 60 bpm) that is associated with complaints of dizziness, nausea, or feeling faint.
- Syncope.
- Slurred speech and/or confusion.
- Any other condition that the site PI judges to unduly increase the risk to the subject.

Infusion related reactions to monoclonal antibodies typically develop within 30 minutes to two hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The most common signs and symptoms of infusion reactions are:

- Fever and/or shaking chills
- Flushing and/or itching
- Alterations in heart rate and BP
- Shortness of breath, chest discomfort
- Nausea, vomiting, and/or diarrhea
- Various types of skin rashes.

In case of a suspected infusion-related reaction, the infusion can be stopped for up to 15 minutes and the subject observed to determine the severity of the reactions. For grading of infusion-related reactions, refer to Appendix B and NCI CTCAE, Version 5.0 – November 2017; see MOP for specific instructions regarding intervention. The decision to continue the infusion is based on the assessment by the investigator; depending on the assessment of the subject, supportive care can be administered, and/or the infusion permanently stopped.

The study may also be suspended (subject enrollment and/or study interventions suspended) because of safety findings, such as an SAE or an overall pattern of symptomatic, clinical, or laboratory events that the DMID Medical Monitor or the SMC consider associated with the study product. These may appear minor in terms of individual events, but might collectively represent potential concern for safety.

The DMID Medical Monitor may stop enrollment and/or administration of study product if AEs that meet the halting criteria are reported.

8.7 Safety Oversight (SRC, SMC)

8.7.1 Data and Safety Monitoring Board

Not applicable

8.7.2 Safety Review Committee

The SRC will consist of a DMID Medical Monitor, Evotec medical officer, and the study/clinical site PIs. The SRC will review blinded combined safety data after each cohort.

Safety data may include, but is not limited to, vital signs, safety laboratory assessments, AEs, physical exam findings, and any noted trends through Day 14 for current cohort. The site PI(s) review the data in real time and share findings with the DMID MM and Evotec medical officer. The PI will indicate whether any cohort dose escalation halting rules or study halting criteria have been met and will provide a recommendation for dose escalation. Ad hoc SMC may be convened at recommendation of SRC in response to a safety issue.

8.7.3 Safety Monitoring Committee

A SMC will be utilized for this study and will be comprised of individuals independent of the study, with relevant expertise, to advise DMID and the study investigators, will be established by DMID. SMC members will be separate and independent of study personnel participating in this study and should not have scientific, financial, or other conflicts of interest related to the study. The SMC will consist of members with appropriate expertise to contribute to the interpretation of the data from this study. The SMC will operate under the rules of a DMID-approved charter. DMID or the SMC chair may convene the SMC at specified times during the course of study as defined in the SMC Charter, or on an ad hoc basis according to protocol criteria, or if there are immediate concerns regarding observations during the course of the study. The SMC for this study will review data at the following time points:

- Organization meeting prior to the start of the study
- Ad hoc review: In response to a safety issue such as a study-halting or dose-escalation-halting rule being met.
- Final Data Review: An end of study summary of cumulative safety data will be provided for electronic review unless the SMC determines a data review teleconference is required.

After each meeting the SMC will make written recommendations to DMID whether the study (or intervention for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be modified and then proceed, or be terminated.

9 HUMAN SUBJECTS PROTECTION

9.1 Institutional Review Board/Independent Ethics Committee

This protocol, the ICF, and all relevant supporting information must be submitted by each site PI to the IRB/IEC for approval. The protocol, ICF, and any advertisement used to recruit study subjects must be approved by the IRB/IEC. Approval by the IRB/IEC of the protocol and ICF must be obtained before the study may be initiated.

The investigator is responsible for informing the IRB/IEC of any changes made to the protocol and to advise them, at least once a year, about the progress of the study. The investigator is also responsible for notifying the IRB/IEC of any significant AEs that occur during the study.

The site PI will obtain IRB approval for this protocol to be conducted at each clinical site and send supporting documentation to the DMID before initiating recruitment of subjects at the site. The investigator will submit applicable information to the IRB/IEC on which it relies for the review and will conduct the review in accordance with 45 CFR 46, ICH E6 GCP, and as applicable, 21 CFR 56 (IRBs) and 21 CFR 50 (protection of human subjects), and other Federal, State, and Local Regulations. The IRB/IEC must be registered with OHRP as applicable to the research. DMID must receive the documentation that verifies IRB/IEC approval for this protocol, associated informed consent documents, and upon request, any recruitment material and handouts or surveys intended for the subjects, prior to the recruitment and enrollment of subjects.

Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and follow-up of subjects and may cease if annual review is no longer required by applicable regulations. The investigator will notify the IRB/IEC of deviations from the protocol and reportable SAEs, as applicable to the IRB/IEC policy.

Each institution engaged in this research will hold a current FWA issued by the OHRP for federally funded research.

A single IRB of record will be accountable for compliance with regulatory requirements for this multi-site study, at participating sites. A formal Reliance Agreement will be required between the single IRB and participating sites. The formal Reliance Agreement will set forth the specific responsibilities of the IRB and each participating site. Participating sites will then rely on the

IRB of record to satisfy the regulatory requirements relevant to the IRB review. Participating sites will maintain essential required documentation of IRB reviews, approvals, and correspondence, and must provide copies of any agreements and essential documentation to the DMID/SDCC or regulatory authorities upon request.

9.2 Informed Consent Process

This study will be conducted in compliance with ICH E6 GCP: Consolidated Guidelines pertaining to informed consent. Subjects will give written consent to participate in the study at the first visit, before initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. The subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled. The ICF must be signed and dated by the subject before study participation. A copy of the ICF must be provided to the subject. Signed consent forms must remain in the subject's study file and be available for verification by the sponsor at any time.

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

An investigator or designee will describe the protocol to potential subjects face-to-face. The key information about the purpose of the study, the procedures and experimental aspects of the study, risks and discomforts, any expected benefits to the subject, and alternative treatment will be presented first to the subject.

Subjects will also receive an explanation that the trial involves research and a detailed summary of the proposed study procedures and study interventions/products. This will include aspects of the trial that are experimental, the probability for random assignment to treatment groups, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), the expected duration of the subject's participation in the trial, alternative procedures that may be available, and the important potential benefits and risks of these available alternative procedures.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Subjects will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. Subjects will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (eg, the investigator) for answers to any questions relating to the research project.

Illiterate Subjects

If illiterate, subjects will be consented using a short form consent that states the required elements of informed consent have been presented to the subject, with a witness present.

9.3 Consent for Future Use of Stored Specimens and Data

No residual biological samples or data will be retained for future use.

9.4 Exclusion of Women, Minorities, and Children (Special Populations)

Women who are pregnant and/or nursing and children will be excluded from this study as the risks of the study product during pregnancy and nursing and in children have not been evaluated.

9.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsors and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study. No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of the DMID and the subject. Subject confidentiality will be maintained when study results are published or discussed in

conferences. The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All records will be kept locked, and all computer entry and networking programs will be carried out with coded numbers only and with password-protected systems. All nonclinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

9.6 Certificate of Confidentiality

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any Federal, State, or Local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the FDA.

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, *or* for the purposes of other research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

9.7 Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject, subject's insurance, or third party. Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the IRB's policies and procedures and subject to IRB approval.

If it is determined by the site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided to the subject by the NIAID, NIH for any injury suffered due to participation in this trial.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

There are no formal hypotheses being tested in this Phase 1 study. The objectives of this study are to evaluate the safety, PK, and immunogenicity profiles of single ascending doses of IV SAR440894 in healthy adults.

10.2 Sample Size Considerations

No formal sample-size calculations based on testing a statistical hypothesis were performed. This study plans to randomize 40 subjects. The number of subjects was selected to allow sufficient evaluation of safety, and PK of the various single dose regimens to be administered in this study and is consistent with standards of practice for Phase 1 studies.

10.3 Treatment Assignment Procedures

10.3.1 Randomization Procedures

This is a Phase 1, randomized, double-blinded, placebo-controlled, multi-site study that will randomize subjects within 5 cohorts to either SAR440894 or placebo in an overall 3:1 ratio (Table 3-1). For each cohort, the first 2 sentinel subjects will be randomized in a 1:1 ratio to SAR440894 and placebo to ensure that 1 of the first 2 subjects receives IV infusion of SAR440894 and the other IV placebo. The remaining 6 subjects in each cohort will be randomized in a 5:1 ratio to SAR440894 and placebo after confirmation that sentinel subject halting rules have not been met. If replacements are needed, each replacement subject will receive the same treatment as the originally randomized subject.

Randomized treatment assignments will be generated by a statistician at Emmes, the SDCC for this study. Subjects will be registered using a web-based application developed by Emmes.

After informed consent has been obtained and study eligibility has been established, subjects will be admitted to the clinical site within approximately 24 hours before the first dose of study product is administered. Randomization will occur following admission to the unit and confirmation of eligibility.

Per ICH guideline E6: GCP, Screening records will be kept at the participating site to document the reason why an individual was screened but failed trial entry criteria. The reasons why individuals failed Screening will be recorded in the SDCC Advantage eClinical® (electronic data capture system).

Enrollment of subjects will be done online using the registration module of Advantage eClinical®. The randomization code will be prepared by statisticians at the SDCC and included in the registration module for this trial. Advantage eClinical® will assign each subject to a treatment arm after the demographic and eligibility data have been entered into the system. A designated individual at the participating site will be provided with a code list, which will be kept in a secure place, for emergency unblinding purposes.

Instructions for use of the registration module are included in the Advantage eClinical® User's Guide. Manual back-up procedures and instructions are provided for use in the event that a participating site temporarily loses access to the Internet or the online enrollment system is unavailable.

10.3.2 Masking Procedures

All study personnel, including the sponsor, site investigators, study personnel involved in study conduct, and subjects will remain blinded to study product assignment until the study is completed and the database is locked, with the exception of the SDCC and pharmacist to prepare drug and monitor drug accountability during the study, and cases in which unblinding is required due to a safety issue. To maintain study blinding, study product preparation will be performed by an unblinded site pharmacist (or qualified unblinded personnel not involved with study procedures or evaluations, at the study site). If unblinding is necessary to maintain subject safety, an unblinded statistician may be engaged to confirm if any of the impacted subjects were administered SAR440894.

Instructions for study product preparation and dosing are outlined in the MOP, provided separately to the site. If the dose level is determined to have safety concerns, the study product assignment for the subjects with the safety issue may be unblinded. The sponsor may also independently decide to unblind the entire cohort or terminate enrollment. In the case of a medical emergency requiring the site PI to know the identity of the study product, the site PI will follow the procedures outlined in Section 10.3.3.

The SMC may receive data in aggregate and presented by cohort. The SMC will review grouped (by treatment) and unblinded data in closed session only.

Blinding of bioanalytical staff will be achieved through use of the SDCC GlobalTrace electronic specimen tracking system in combination with unique sample barcodes. The system provides all trial specimens with a masked label (barcode) in order to blind both the DMID CAR and the laboratories that receive trial specimens. This masked label ensures the integrity of the data. Custom specimen labels that eliminate this safeguard (eg, labels that include the subject ID and/or time point) will not be used. Further details will be described in the MOP.

10.3.3 Breaking the Blind

This study is a double-blind design. The site PI, study personnel, and subjects will not make any effort to determine which study product is being received. Unblinded pharmacy personnel or unblinded study personnel (ie, PK analyst and statistician) may be utilized in this study. Only in the case of an emergency, when knowledge of the study product is essential for the clinical management or welfare of a specific subject, may the PI unblind a subject's treatment assignment.

Before any unblinding, the site PI is strongly advised to discuss options with the DMID Medical Monitor or appropriate sponsor study personnel. As soon as possible and without revealing the subject's study product assignment (unless important to the safety of subjects remaining in the study), the PI must notify the sponsor within 24 hours if the blind is broken for any reason and the PI was unable to contact the sponsor before unblinding. The site will record unblinding as a protocol deviation and document the date and reason for revealing the blinded treatment assignment for that subject.

10.4 Planned Interim Analyses

10.4.1 Interim Safety Review

Safety reviews will occur by the SRC and SMC as outlined in Section 8.7. Halting rules are outlined in Section 8.6. Safety will be evaluated by presenting summaries of AEs, clinical laboratory evaluations (hematology evaluation, chemistry and coagulation panel, and urinalysis), vital signs, and ECGs. Safety variables will be tabulated by cohort and presented for all subjects in the safety population.

10.5 Final Analysis Plan

The ICH/FDA Guidance Document E9 (Statistical Principles for Clinical Trials) will be followed for all statistical content. For categorical data, summaries of frequencies and percentages will be

presented. Summaries for continuous data may include minimum, median, mean, SD, and maximum. All data will be summarized separately by dose group and study product. Listings of individual subject data will also be produced. Detailed summaries of the PK, immunogenicity and other analyses will be prospectively described in a statistical analysis plan (SAP) prepared by the SDCC statistician before unblinding of subjects. All final analyses will be performed by the SDCC statistician after the data are locked. Unless specified otherwise in the SAP, missing data will not be imputed.

All subjects receiving placebo will be combined across cohorts into a single placebo group for analysis. Missing data for outcome measures will not be imputed.

10.5.1 Safety Analysis Plan

Safety will be evaluated by presenting summaries of AEs, clinical laboratory evaluations (hematology evaluation, coagulation, chemistry panel, and urinalysis), vital signs, physical exam, and ECGs. Safety variables will be tabulated by dose group and presented for all subjects in the safety population. The safety population will include all subjects who receive any study product and will be grouped by treatment received.

10.5.1.1 Adverse and Serious Adverse Events

Adverse events will be coded using MedDRA Version 25.1 or higher. The incidence of TEAEs will be presented by system organ class, high-level group term, and preferred term according to MedDRA, by relationship to the study product, by severity, and by whether or not they resulted in alteration of administration of or discontinuation of study product. In addition, the incidence of serious TEAEs and TEAEs leading to discontinuation of study product will be presented by system organ class, high-level group term, preferred term, and relationship to study product.

10.5.1.2 Clinical Safety Labs, Vital Signs, and Electrocardiograms

Descriptive statistics for clinical laboratory test results, vital signs, and ECG intervals, including changes from baseline, will be presented by time point and dose group. Baseline is defined as the measurement closest to, but before, the administration of study product. If triplicate measurements were performed at the same visit, then baseline is the mean value of the measurements for the visit closest to, but before, administration of study product. Similarly, for analyses of change from baseline, mean values will be used in the case of replicate measurements at a single visit post baseline. Laboratory results and vital signs obtained after start of dosing will be graded according to criteria Appendix C and Appendix D for subjects who screened and enrolled prior to Protocol Version 11.0 and NCI CTCAE, Version 5.0 –

November 2017 for subjects who screen and enroll with Protocol Version 11.0 and summarized. Summaries of vital signs and ECG assessments will be analyzed at Screening and post dose using descriptive statistics.

10.5.2 Pharmacokinetic Analysis Plan

Details of the PK analysis plan will be included in the SAP. Blood samples from all subjects who received a complete dose of SAR440894 (the PK population) will be analyzed for the concentration of SAR440894 by a validated enzyme-linked immunosorbent assay methodology. Plasma concentration-time curves will be constructed for each subject and each dose group. An optional review of SAR440894 time-concentration trends may be performed following each cohort. For each plasma profile, PK parameters including, but not limited to, half-life, C_{max}, minimum observed plasma concentration (C_{min}), time of the maximum observed plasma concentration (T_{max}), AUC, clearance, and volume of distribution will be estimated by noncompartmental analysis methods using Version 8.0 or higher of Phoenix WinNonlin®.

10.5.3 Immunogenicity Analysis Plan

A positive result will be defined as a positive Screening assay followed by a positive confirmatory assay and a negative result will be defined as a negative Screening assay or a positive Screening assay followed by a negative confirmatory assay. By dose group and post-dose time point, ADA results will be summarized as negative, treatment-induced ADA (negative result at baseline and positive result post-dose), treatment-boosted ADA (positive both at both baseline and post-dose, with a 4-fold or 9-fold increase to titer as defined in the SAP), or pre-existing ADA (ADA present both at baseline and post-dose, but not treatment-boosted). Incidence of ADA (defined as either treatment-induced or treatment-boosted ADA at any time point) will be summarized by dose group. ADA titers may be determined in the case of positive ADA results. If determined, summary statistics ADA titers and possibly fold change from baseline in titer will be summarized by dose group and time point. If five or more subjects have positive ADA results, the effect of ADA on the clearance of SAR440894 may be explored. Additionally, the proportion of subjects with a positive Screening assay result will be summarized by dose group and time point. ADA results may be analyzed between dosing cohorts.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the site is responsible for conducting routine quality assurance and quality control activities to internally monitor study progress and protocol compliance. The site PI will provide direct access to all study-related source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The SDCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

13 DATA HANDLING AND RECORD KEEPING

Each participating site will maintain appropriate medical and research records for this clinical trial, in compliance with ICH E6 GCP Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. The site will permit the study monitor or other authorized representatives of DMID as well as governmental regulatory agencies, such as the FDA, to examine (and when required by applicable law, to copy) clinical trial records for the purposes of quality assurance reviews, audits, monitoring and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files, and records kept at the pharmacy, at the laboratories and medico-technical departments involved in this clinical trial. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the clinical trial.

Interview of subjects is sufficient for obtaining medical history. Solicitation of medical records from the subject's primary care provider is not required.

Training sessions, regular monitoring of investigators by sponsor-designated personnel, instruction manuals, data verification, crosschecking, and data audits will be performed to ensure quality of all study data. Investigator meetings will be performed to prepare investigators and other study personnel for appropriate collection of study data.

13.1 Data Management Responsibilities

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue permanent ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

13.2 Electronic CRF (eCRF)

Copies of the electronic CRF (eCRF) will be provided for use as source data collection forms and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source data collection forms should be consistent or the discrepancies should be explained.

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site PI. During the study, the site PI must maintain complete and accurate documentation for the study.

The SDCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

13.3 Data Capture Methods

Clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical exam findings, and clinical laboratory values), immunogenicity data, and PK data will be entered into a 21 CFR 11-compliant Internet Data Entry System provided by the SDCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the data collection forms or original source completed by the study personnel.

The eCRF will be supplied the SDCC for the recording of all information and study data as specified by this protocol. All eCRFs must be completed by trained study personnel. The investigator is responsible for ensuring that the eCRF data are entered and completed in a timely manner.

13.4 Types of Data

Data for this study will include clinical, safety, immunogenicity, and PK measures.

13.5 Study Records Retention

Study records and reports including, but not limited to, eCRFs, source documents, ICFs, laboratory test results, and medication inventory records, shall be retained for at least 6 years

after the study is completed, but no less than 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. The site must contact DMID for authorization before destroying any study records.

14 CLINICAL MONITORING

Site monitoring is conducted to ensure that the human subjects' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP, and applicable sponsor SOPs. DMID, the sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits (in-person or remote, as appropriate) will be made at intervals defined by the clinical monitoring plan and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, ICFs, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with the site PIs to discuss any problems and actions to be taken, and will document site visit findings and discussions.

15 PUBLICATION POLICY

Following completion of the study, the lead PI is expected to publish the results of this research in a scientific journal. All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

NIH Public Access Policy, http://publicaccess.nih.gov/ NIH Office of Extramural Research Grants and Funding, http://grants.nih.gov/grants/oer.htm

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first subject. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date.

As part of the result posting, a copy of this protocol (and its amendments), and a copy of the Statistical Analysis Plan will be posted on ClincialTrials.gov. For this trial the responsible party is DMID/NIAID/NIH, which will register the trial and post results.

16 LITERATURE REFERENCES

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2. Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. *Expert Rev Clin Immunol*. 2009;5(5):499-521. doi:10.1586/eci.09.31

3. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJT. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov*. 2010;9(4):325-338. doi:10.1038/nrd3003

4. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE); Version 5.0, 27 November 2017.

17 APPENDICES

Appendix A. **SCHEDULE OF EVENTS**

Study Visit	**Screening**[1]	**Admit to Unit**	**Confinement and Infusion**			**Discharge from Unit**	**Follow-Up Visits**						**Final Visit**	**Early Term**	**Unscheduled Visit**
Study Day ±Window	**-45 to -2**	**-1**	**1**	**2**	**3**	**4**	**7 ±1**	**14 ±2**	**28 ±4**	**56 ±4**	**84 ±7**	**112 ±7**	**150 ±7**	**NA**	
Obtain informed consent	X														
Record demographics	X														
Review inclusion/ exclusion criteria	X	X													
Review medical history	X	X	X[12]												X
Review concomitant medications[2]	X	X	X[12]	X	X	X	X	X	X	X	X	X	X	X	X
Review contraception/ menses	X	X	X			X	X	X	X	X	X	X	X	X	
Height/weight/BMI	X	X[16]													
Perform complete physical examination[3]	X	X				X							X	X	
Perform symptom-directed			X[12,13]	X[13]	X[13]		X	X	X	X	X	X			X

Study Visit	**Screening**[1]	**Admit to Unit**	**Confinement and Infusion**			**Discharge from Unit**	**Follow-Up Visits**						**Final Visit**	**Early Term**	**Unscheduled Visit**
Study Day ±Window	**-45 to -2**	**-1**	**1**	**2**	**3**	**4**	**7 ±1**	**14 ±2**	**28 ±4**	**56 ±4**	**84 ±7**	**112 ±7**	**150 ±7**	**NA**	
physical examination															
Obtain vital signs[4]	X	X	X[12,14]	X[4]	X[4]	X	X	X	X	X	X	X	X	X	X
Obtain Screening labs[5]	X														
Obtain clinical safety labs[6]		X		X	X	X	X	X	X	X	X	X	X	X	
Renal injury biomarker (serum cystatin-C)		X		X	X	X	X	X	X	X	X	X	X	X	
Serum β-hCG[7]	X	X													
Urine pregnancy test									X		X		X	X	
Urine dipstick[8]	X	X		X	X	X	X	X	X	X	X	X	X	X	
Urine toxicology	X	X													
Breathalyzer	X	X													
Immunogenicity (ADA)			X[12]							X		X	X	X	
Hypersensitivity panel			X[12,15]											X[15]	
12-lead ECG[9]	X		X			X							X	X	
Viral serology[10]	X														

Study Visit	**Screening**[1]	**Admit to Unit**	**Confinement and Infusion**			**Discharge from Unit**	**Follow-Up Visits**						**Final Visit**	**Early Term**	**Unscheduled Visit**
Study Day ±Window	**-45 to -2**	**-1**	**1**	**2**	**3**	**4**	**7 ±1**	**14 ±2**	**28 ±4**	**56 ±4**	**84 ±7**	**112 ±7**	**150 ±7**	**NA**	
Obtain PK samples[11]			X	X	X	X	X	X	X	X	X	X	X	X	
Randomization		X													
Study product administration			X												
Counsel on the avoidance of pregnancy and prohibited medications/ substances	X					X	X	X	X	X	X	X		X	
Counsel on avoidance of vaccines						X	X	X	X	X					
AE review			X	X	X	X	X	X	X	X	X	X	X	X	
SAE review			X	X	X	X	X	X	X	X	X	X	X	X	

1. Screening will be completed within 45 days prior to administration of study product and may require more than one visit.
2. Concomitant medications including all of the following: prescription drugs, over-the–counter drugs, herbs, vitamins, nutritional supplements, illicit and recreational substance use, vaccines, birth control information.
3. Complete physical examination includes general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, lymph nodes.
4. Vital signs include supine diastolic and systolic BP, heart rate, respiratory rate and oral temperature. Vital signs will be collected in singlicate unless part of AE/SAE assessment. If AE/SAE involving BP or heart rate occurs, vital signs will be collected in triplicate from the same arm at least 5 minutes apart. At Screening and on Days -1, 2, 3, and all Follow up visits, measure vital signs prior to blood collection.

5. Screening laboratory tests are outlined in Table 7-1 and Section 6.2.
6. Clinical safety laboratory tests are outlined in Table 7-1, Section 6.3, and Section 6.4.
7. A serum pregnancy test will be obtained for all women of reproductive capacity at Screening and within approximately 24 hours before study product administration. Results must be confirmed as negative before study product infusion begins. An FSH level will be checked in female participants reporting postmenopausal status.
8. A urine dipstick will be done to evaluate for presence of protein, glucose, or blood in urine. If dipstick is abnormal, a complete urinalysis with microscopy will be performed.
9. A 12-lead ECG will be done during Screening (triplicate), within 60-minutes prior to dosing (triplicate), at the end of the infusion of the study product +15 minutes (triplicate, ±5 minutes), and prior to discharge (triplicate). Continuous remote telemetry monitoring will be conducted from 30 minutes prior to study product administration to approximately 4 hours post dose.
10. Viral serology includes CHIKV antibody, HIV antibody, HB surface antigen and antibody to HCV.
11. Plasma PK samples will be taken at the following times with an acceptable window of 60-minutes prior to dosing; ±10 minutes in the first 8 hours after dosing; and ±30 minutes between 9 and 72 hours: within 5 minutes of the completion of the infusion, and at: 1, 4, 8, 12, 24, 48, and 72 hours relative to the end of the infusion time, and on Day 7 ±1, Day 14 ±2, Day 28 ±4, Day 56 ±4, Day 84 ±7, Day 112 ±7, Day 150 ±7, and ET (if needed). PK samples at Follow-up visits will be collected during the designated Follow-up window.
12. Occurs prior to dosing on Day 1 and is considered to be the baseline sample.
13. A symptom-directed physical exam will be performed prior to infusion and after (as needed) to assess potential/active AEs and signs and symptoms of infusion reactions.
14. Vital signs will be checked within a 60-minute period prior to dosing and every 15 minutes (±5 minutes) during the infusion. After the infusion, vital signs will be taken at the following time points: 1, 2, 4, and 6 hours with an acceptable window of ±5 minutes for each time point.
15. Draw 12 mL prior to dosing. If a subject develops anaphylaxis or anaphylactoid reaction, three additional 12 mL samples will be collected: during onset, 2 or more hours after onset, and after resolution of symptoms.
16. Measure only weight on Day -1. Day -1 weight will be used for dose calculations.

Appendix B. **TOXICITY TABLE**

Clinical Adverse Events			
CARDIOVASCULAR TOXICITY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Arrhythmia[1]	N/A	Asymptomatic; transient signs; no medical intervention required	Recurrent/persistent; symptomatic medical intervention required
Hemorrhage, Blood Loss	Estimated blood loss ≤ 100 mL	Estimated blood loss > 100 mL, no transfusion required	Transfusion required
QTc (Fridericia's correction)[2]	**Females:** QTc interval > 470-479 msec	QTc interval 480 to 499 msec OR Increase in interval 30-50 msec above baseline	QTc interval ≥ 500 msec OR Increase in interval > 50 msec above baseline
	Males: Asymptomatic, QTc interval > 450-479 msec		
RESPIRATORY TOXICITY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Cough	Transient; no treatment	Persistent cough	Interferes with daily activities
Bronchospasm, Acute	Transient; no treatment; 71% - 80% FEV1 of predicted peak flow	Requires medical intervention; normalizes with bronchodilator; FEV1 60% - 70% (of predicted peak flow)	No normalization with bronchodilator; FEV1 < 60% of predicted peak flow
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities; no treatment	Prevents daily and usual social activity OR requires treatment

[1] Sinus arrhythmia is a normal variant and will not be considered an adverse event.
[2] Inclusion dependent upon protocol requirements.

GASTROINTESTINAL TOXICITY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity OR 1 - 2 episodes/24 hours	Some interference with activity OR > 2 episodes/24 hours	Prevents daily activity OR requires IV hydration OR requires medical intervention
Diarrhea	2 - 3 loose or watery stools or < 400 gm/24 hours	4 - 5 loose or watery stools or 400 – 800 gm/24 hours	6 or more loose or watery stools or > 800 gm/24 hours OR requires IV hydration OR requires medical intervention
LOCAL REACTIONS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever for more than 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Tenderness	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Erythema or Redness (measure local reaction at the greatest single diameter)	25 - 50 mm	51 - 100 mm	> 100 mm
Induration or Swelling	25 - 50 mm and does not interfere with activity	51 - 100 mm or interferes with activity	> 100 mm or prevents daily activity
SYSTEMIC REACTIONS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Allergic Reaction	Pruritus without rash	Localized urticaria OR requires oral therapy	Generalized urticaria; angioedema OR anaphylaxis OR requires epinephrine

Infusion Related Reaction (Cytokine Release Syndrome)	Mild transient reaction, and Infusion interruption (ie, antibody infusion) not indicated	Infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS); prophylactic medication indicated for ≤ 24 hours	Prolonged severe signs and symptoms or Recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours OR some interference with activity	Significant; any use of narcotic pain reliever OR prevents daily activity OR requires triptans
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
All Other Conditions	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Illness or Clinical Adverse Event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention

Note: This toxicity table is to be used for subjects who screened and enrolled prior to Protocol Version 11.0. Subjects who screen and enroll with Protocol Version 11.0, toxicity will be assessed with the NCI CTCAE, Version 5.0 – November 2017.

Appendix C. LABORATORY AND VITAL SIGNS ELIGIBILITY RANGES AND TOXICITY RANGES

For use by Duke Clinical Laboratory

	Reference Range [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
Blood, Serum, or Plasma Chemistries [d]					
Sodium (mmol/L)	135 – 145	LO	< LLN - 132	131 - 130	< 130
		HI	> ULN - 148	149 - 150	> 150
Potassium (mmol/L)	3.5 - 5.0	LO	< LLN - 3.1	< 3.1 - 3.0	< 3.0
		HI	> ULN - 5.2	5.3 - 5.4	> 5.4
Bicarbonate/CO2 (mmol/L)	21 – 30	LO	20 - 17	16 - 12	< 12
		HI	31 - 35	36 - 40	> 40
Glucose (mg/dL)	70 - 99 [e]	LO	69 - 65	64 - 55	< 55
		HI	> ULN - 120	121 - 130	> 130
	70 – 140 [f]	HI	141 - 159	160 - 200	> 200
Blood Urea Nitrogen (mg/dL)	7 – 20	HI	21 - 26	27 - 31	> 31
Creatinine (mg/dL)	Female: 0.4 – 1.0	HI	> ULN - 1.7	1.8 - 2.0	> 2.0
	Male: 0.6 – 1.3				
eGFR (mL/min/1.73 m^2) by Modification of Diet in Renal Disease (MDRD) equation	≥ 60 mL/min/1.73 m^2	LO	59 - 45	44 - 30	< 30
Calcium (mg/dL)	8.7 - 10.2	LO	< LLN - 8.0	7.9 - 7.5	< 7.5
		HI	> ULN - 11.0	11.1 - 11.5	> 11.5
Albumin (g/dL)	3.5 - 4.8	LO	3.4 - 2.8	2.7 - 2.5	< 2.5
Total Protein (g/dL)	6.2 – 8.1	LO	< LLN - 5.5	5.4 - 5.0	< 5.0
Alkaline Phosphatase (U/L)	24 – 110	N	111 - 240	241 - 360	> 360

	Reference Range [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
AST (U/L)	15 – 41	HI	42 - 105	106 - 175	> 175
ALT (U/L)	Female: 14 -54	HI	55 – 105	106 – 175	>175
	Male: 17 -63	HI	64 - 105	106 - 175	> 175
Bilirubin, Serum Total (mg/dL)	0.4 – 1.5	HI	1.6 - 2.0	2.1 - 2.5	> 2.5
Hematology [d]					
Hemoglobin (g/dL)					
Females	12.0 – 15.5	LO	11.9 - 11.0	10.9 - 9.5	< 9.5
Males	13.7 – 17.3	LO	13.6 - 12.0	11.9 - 10.0	< 10.0
WBC ($10^{9/L}$)	3.2 – 9.8	LO	3.19 - 2.50	2.49 - 1.50	< 1.50
		HI	9.90 – 14.99	15.00 - 20.00	> 20.00
Lymphocytes (10^9/L)	0.6 – 4.2	LO	0.59 – 0.50	0.49 - 0.40	< 0.40
Neutrophils (10^9/L)	2.0 – 8.6	LO	1.99 - 1.50	1.49 - 1.00	< 1.00
Eosinophils (10^9)/L	0.00-0.70	HI	0.71 - 0.75	0.76 - 1.50	> 1.50
Platelets (10^9/L)	150 – 450	LO	149 - 120	119 - 100	< 100
Coagulation					
Prothrombin Time (seconds)	9.5 – 13.1	HI	> ULN - 14.4	14.5 - 15.7	> 15.7
Prothrombin INR	0.9 – 1.1	HI	1.2-1.4	1.5-2.0	>2.0
Partial Thromboplastin Time (seconds)	26.8 – 37.1	HI	> ULN - 42.1	42.2 - 50.0	> 50.0
Urine					
Protein	Negative	HI	1+	2+	> 2+
Glucose	Negative	HI	1+	2+	> 2+
Bilirubin	Negative	HI	1+	2+	> 2+
Nitrite	Negative	HI	Positive	N/A	N/A
Blood (microscopic)—red blood cells per high power field (rbc/hpf)	0 – 3	HI	4 - 10	11 - 50	> 50 and/or gross blood

	Reference Range [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
WBC (microscopic)—white blood cells per high power field (wbc/hpf)	0 – 5	HI	6 - 10	11 - 50	> 50 and/or gross blood
Urobilinogen (mg/dL)	0.2 – 1.0	HI	> ULN – 1.5	1.6 – 2.0	> 2.0
Vital Signs					
Fever (°C) [g]		HI	38.0 - 38.4	38.5 - 38.9	> 38.9
Fever (°F) [g]		HI	100.4 - 101.1	101.2 - 102.0	> 102.0
Tachycardia—beats per minute		HI	101 - 115	116 - 130	> 130 or ventricular dysrhythmias
Bradycardia—beats per minute					
Baseline ≥ 60		LO	54 - 50	49 - 45	< 45
Baseline < 60		LO	50 - 45	44 - 40	< 40
Hypertension (systolic)—mm Hg [h]		HI	141 - 150	151 - 160	> 160
Hypertension (diastolic)—mm Hg [h]		HI	91 - 95	96 - 100	> 100
Hypotension (systolic)—mm Hg [h]		LO	89 - 85	84 - 80	< 80
Tachypnea - breaths per minute		HI	23 - 25	26 - 30	> 30

Note: This table is to be used for subjects who screened and enrolled prior to Protocol Version 11.0. Subjects who screen and enroll with Protocol Version 11.0, toxicity will be assessed with the NCI CTCAE, Version 5.0 – November 2017.

[a] Reference range of Duke Clinical laboratory.
[b] High, Low, Not Graded.
[c] If initial bound of Grade 1 has gap from reference range, calculations based on *New England Journal of Medicine* reference ranges.
[d] Depending upon the lab used, references ranges and grading may be split out by sex and/or age.
[e] Fasting ≥ 8hours
[f] Non-fasting; includes subjects fasting ≥ 2 hours and < 8 hours.
[g] Oral temperature. A protocol should select either °C or °F for inclusion.
[h] Assuming subject is awake, resting, and supine; for adverse event, 3 measurements on the same arm with concordant results.

Appendix D. LABORATORY ELIGIBILITY AND TOXICITY RANGES

For use by DEPRU Core Laboratory

	Reference Range	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
Blood, Serum, or Plasma Chemistries [d]					
Sodium (mmol/L)	135 – 146	LO	< LLN - 132	131 - 130	< 130
		HI	> ULN - 148	149 - 150	> 150
Potassium (mmol/L)	3.4 – 4.6	LO	< LLN - 3.1	< 3.1 - 3.0	< 3.0
		HI	> ULN - 5.2	5.3 - 5.4	> 5.4
Bicarbonate/CO2 (mmol/L)	23 – 34	LO	22 - 17	16 - 12	< 12
		HI	> ULN - 35	36 - 40	> 40
Glucose (mg/dL)	70 - 99 [e]	LO	69 - 65	64 - 55	< 55
		HI	> ULN - 120	121 - 130	> 130
	70 – 140 [f]	HI	141 - 159	160 - 200	> 200
Blood Urea Nitrogen (mg/dL)	5-37	HI	> ULN - 41	42-46	> 46
Creatinine (mg/dL)	0.5 – 1.2	HI	> ULN - 1.7	1.8 - 2.0	> 2.0
eGFR (mL/min/1.73 m^2) by Modification of Diet in Renal Disease (MDRD) equation	≥ 60 mL/min/1.73 m^2	LO	59 - 45	44 - 30	< 30
Calcium (mg/dL)	8.3 - 10.6	LO	< LLN - 8.0	7.9 - 7.5	< 7.5
		HI	> ULN - 11.0	11.1 - 11.5	> 11.5
Albumin (g/dL)	3.8 - 5.1	LO	3.7 - 2.8	2.7 - 2.5	< 2.5
Total Protein (g/dL)	5.9 – 8.3	LO	< LLN - 5.5	5.4 - 5.0	< 5.0
Alkaline Phosphatase (U/L)	34 – 138	N	139 - 240	241 - 360	> 360

	Reference Range	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
AST (U/L)	6 – 40	HI	41 - 105	106 - 175	> 175
ALT (U/L)	Female: 6-35	HI	36 – 105	106 – 175	> 175
	Male: 6-40	HI	41 - 105	106 - 175	> 175
Bilirubin, Serum Total (mg/dL)	0.2-1.0	HI	1.1 - 2.0	2.1 - 2.5	> 2.5
Hematology [d]					
Hemoglobin (g/dL)					
Females	12.0 – 15.5	LO	11.9 - 11.0	10.9 - 9.5	< 9.5
Males	13.7 – 17.3	LO	13.6 - 12.0	11.9 - 10.0	< 10.0
WBC ($10^{9/L}$)	3.2 – 9.8	LO	3.19 - 2.50	2.49 - 1.50	< 1.50
		HI	9.90 – 14.99	15.00 - 20.00	> 20.00
Lymphocytes (10^9/L)	0.6 – 4.2	LO	0.59 – 0.50	0.49 - 0.40	< 0.40
Neutrophils (10^9/L)	2.0 – 8.6	LO	1.99 - 1.50	1.49 - 1.00	< 1.00
Eosinophils (10^9)/L	0.00-0.70	HI	0.71 - 0.75	0.76 - 1.50	> 1.50
Platelets (10^9/L)	150 – 450	LO	149 - 120	119 - 100	< 100
Urine					
Protein	Negative	HI	1+	2+	> 2+
Glucose	Negative	HI	1+	2+	> 2+
Bilirubin	Negative	HI	1+	2+	> 2+
Nitrite	Negative	HI	Positive	N/A	N/A
Blood (microscopic)—red blood cells per high power field (rbc/hpf)	0 – 3	HI	4 - 10	11 - 50	> 50 and/or gross blood
WBC (microscopic)—white blood cells per high power field (wbc/hpf)	0 – 5	HI	6 - 10	11 - 50	> 50 and/or gross blood
Urobilinogen (mg/dL)	0.2 – 1.0	HI	> ULN – 1.5	1.6 – 2.0	> 2.0

	Reference Range	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)

Note: This table is to be used for subjects who screened and enrolled prior to Protocol Version 11.0. Subjects who screen and enroll with Protocol Version 11.0, toxicity will be assessed with the NCI CTCAE, Version 5.0 – November 2017.

[a] Reference range of DEPRU Core laboratory.
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[c] If initial bound of Grade 1 has gap from reference range, calculations based on *New England Journal of Medicine* reference ranges.
[d] Depending upon the lab used, references ranges and grading may be split out by sex and/or age.
[e] Fasting $\geq$ 8 hours
[f] Nonfasting; includes subjects fasting $\geq$ 2 hours and < 8 hours.