A Phase 1, Three-Part, Randomized, Double-Blind, Single and Multiple Subcutaneous Dose Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of Rezafungin in Healthy Adult Subjects

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Lead Principal Investigator: Dennis Ruff, MD

DMID Clinical Project Manager: Maureen Mehigan, RN

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STATEMENT OF ASSURANCE

Each Institution will hold a current Federal Wide Assurance (FWA) issued by the Office for 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 Code of Federal Regulations (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

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

United States (US) 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 (IRBs), 21 CFR Part 11(Electronic Records and Electronic Signatures), and 21 CFR Part 312 (Investigational New Drug Application)

International Conference on Harmonization: GCP (ICH E6); 62 Federal Register 25691 (1997); and revisions

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

SIGNATURE PAGE

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Protocol Number: 17-0088

Protocol Version (Issue Date):

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 GCP guidelines.

I agree to conduct this trial in compliance with GCP and applicable regulatory requirements.

I agree to conduct this trial 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 Principal Investigator Signature:

Signed: _____ Date: 07/Apr/2020

Dennis Ruff, MD

Site Principal Investigator

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LIST OF ABBREVIATIONS

λ_z	Apparent first-order terminal elimination rate constant
AE	Adverse Event/Adverse Experience
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AmB	Amphotericin B
AR	Accumulation ratio
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
AUC_{inf}	Area under the plasma concentration versus time curve from time 0 to infinite time
AUC_{last}	Area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration
AV	Atrioventricular block
BA	Bioavailability
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CK	Creatine Kinase
CL	Total clearance
CL/F	Apparent clearance
C_{max}	Maximum measured plasma concentration

CMS	Clinical Materials Services
CROMS	Clinical Research Operations and Management Support
CRU	Clinical Research Unit
DCF	Data Collection Form(s)
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FEV	Forced expiratory volume
FU	Follow-Up
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFIs	Invasive Fungal Infections
IND	Investigational New Drug Application
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ISM	Independent Safety Monitor

IV	Intravenous
LC-MS/MS	Liquid Chromatography-Mass Spectrometry/Mass Spectrometry
MAD	Multiple Ascending Dose
MedDRA®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MTD	Maximum tolerated dose
N	Number (typically refers to subjects)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PCP	*Pneumocystis* pneumonia
PE	Physical Examination
PI	Principal Investigator
PK	Pharmacokinetics
PR (interval)	Interval measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by electrocardiogram
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control
QRS (interval)	The interval between the Q wave and the S wave in the heart's electrical cycle as measured by electrocardiogram; principal deflection in the electrocardiogram

QT (interval)	A measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by electrocardiogram
QTc (interval)	A measure of time between the start of the Q wave and the end of the T wave in the heart's electrical cycle measured by electrocardiogram corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
SAD	Single Ascending Dose
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SC	Subcutaneous
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Classes
SOP	Standard Operating Procedure
$t_{1/2}$	Terminal phase half-life
T_{max}	Time to reach maximum measured plasma concentration
TMP/SMX	Trimethoprim/Sulfamethoxazole
US	United States
USP	United States Pharmacopeia
VCT	Verified Clinical Trials
V_{ss} or V_z/F	Volume of distribution (adjusted for bioavailability)
WBC	White Blood Cell

PROTOCOL SUMMARY

Title:	A Phase 1, Three-Part, Randomized, Double-Blind, Single and Multiple Subcutaneous Dose Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of Rezafungin in Healthy Adult Subjects
Design of the Study:	This is a Phase 1, double-blind, placebo-controlled trial in three parts. A single ascending dose (SAD) study in six cohorts receiving a single subcutaneous (SC) dose of 1, 10, 30, 60, 100, or 200 mg of rezafungin; a multiple ascending dose (MAD) study in four cohorts receiving 30 mg x 3 doses, 60 x 3 doses, 100 mg x 3 doses, or 200 mg x 3 doses of rezafungin SC with dosing frequency of once every 7 days; and a two-period cross-over bioavailability (BA) study receiving 100 mg of rezafungin. The two-period cross-over BA study will be assessed unblinded in two sequences (10 subjects, 100 mg or maximum tolerated dose (MTD) of rezafungin in Part 1); 5 subjects will receive an SC injection of rezafungin in Period 1 followed by an intravenous (IV) infusion of rezafungin in Period 2, and 5 subjects will receive an IV infusion of rezafungin in Period 1 followed by an SC injection of rezafungin in Period 2. Each SAD (except cohort 1) and MAD cohort will contain 8 subjects (6 subjects will receive a SC injection of rezafungin, and 2 subjects will receive placebo). Each SAD (except cohort 1) and MAD cohort will be conducted with sentinel dosing. SAD cohort 1 will be comprised of 4 subjects (3:1 rezafungin to placebo) with no sentinel dosing. Parts 2 and 3 of the study will only be conducted after FDA review for safety data and PK data from all subjects participating in Part 1; Part 3 may be run in parallel with the first cohort (Cohort 7) of Part 2.

Study Phase:	1
Study Population:	Approximately 86 healthy male and female subjects, aged 18-45 years (inclusive)
Number of Sites:	1
Description of Study Product or Intervention:	Subcutaneous formulation: Rezafungin for Injection, Subcutaneous Use, 100 mg/mL, is a sterile liquid product supplied in single-dose vials containing 1.0 mL of extractable volume. The active pharmaceutical ingredient is rezafungin acetate, a water-soluble amorphous acetate salt. The inactive ingredient is mannitol. Intravenous (IV) formulation: Rezafungin for Injection, 200 mg/vial, is a sterile product supplied as a white to pale yellow lyophilized powder in single-dose glass vials for reconstitution with Sterile Water for Injection, United States Pharmacopeia (USP). The reconstituted product is diluted in sterile, 0.9% Sodium Chloride Injection, USP for IV infusion. The active pharmaceutical ingredient is rezafungin acetate, a water-soluble amorphous acetate salt. The inactive ingredients include excipients of mannitol, polysorbate 80, and histidine. Placebo is 5% Dextrose Injection, USP, a sterile, nonpyrogenic solution of dextrose in water for injection. The solution has the osmolarity of 252 mOsmol/L, which is slightly hypotonic. For 1 mg subcutaneous doses, the Subcutaneous formulation will be diluted 1:10 in 5% Dextrose Injection, USP prior to administration. The diluent solution, 5% Dextrose Injection, USP is a sterile and nonpyrogenic parenteral solution. Reconstitution solution is Sterile Water for Injection, WFI, USP, which is a clear, colorless solution.

Study Objectives:	Primary: • To determine the safety and tolerability of single-ascending SC doses (SAD) of rezafungin. • To determine the safety and tolerability of multiple-ascending SC doses (MAD) of rezafungin. • To determine the pharmacokinetic (PK) profile in plasma of rezafungin in healthy adult subjects; Secondary: To evaluate the bioavailability (BA) of rezafungin when administered by SC injection relative to IV infusion in healthy adult subjects.

Outcome Measures	Primary: SAD Safety will be assessed by adverse events and serious adverse events (SAEs) from start of dosing to Day 30, clinical laboratory tests at baseline and from Day 2 to Day 30, ECGs at Screening and post-dose on Days 1, 7, and 30, physical exams at baseline and post-dose on Day 1 to Day 30, vital signs at baseline and from Day 1 to Day 30, and injection site evaluation from dosing to Day 30. Tolerability will be assessed by occurrence of solicited local reactogenicity (injection site evaluation) from dosing to Day 30. MAD Safety will be evaluated for multiple-ascending SC doses (MAD) of rezafungin. Safety will be assessed by adverse events and SAEs from start of dosing to Day 45, clinical laboratory tests at baseline and from Day 2 to Day 45, ECGs at Screening and post-dose on Days 1, 8, 15, 21, 30, and 45, physical exams at baseline to Day 45, and vital signs at baseline to Day 45. Tolerability will be assessed by occurrence of solicited local reactogenicity (injection site evaluation) from first dose to Day 45. PK Pharmacokinetic (PK) profiles of rezafungin will be assessed by measurement of drug levels in plasma after SC administration in each cohort. Plasma for PK analysis will be collected at planned timepoints up to Day 30 in the SAD cohorts, and Day 45 in the

	MAD cohorts. PK parameters will be estimated from the rezafungin plasma concentration-time data. Secondary: The BA of rezafungin when administered by SC injection relative to IV infusion will be assessed by measurement of drug levels in plasma after administration by SC injection or by IV infusion in each cross over period. Plasma samples will be collected at planned timepoints up to Day 52 for Part 3/BA The absolute BA will be calculated as the ratio of AUC for the SC injection and AUC for the IV infusion of administration.
Duration of Individual Subject Participation:	Part 1 SAD: Individual subjects will participate for approximately 58 days, including up to 28 days for screening and 30 days for dosing and follow-up (FU). Part 2 MAD: Individual subjects will participate for approximately 73 days, including up to 28 days for screening and 45 days for dosing and FU. Part 3 BA: Individual subjects will participate for approximately 80 days, including up to 28 days for screening and 52 days for dosing and FU.
Estimated Time to Last Subject/Last Study Day:	Approximately 30 months

Figure 1

Study Schematic - SAD Study (Part 1) Cohorts 1, 2, 3, 4, 5, and 6

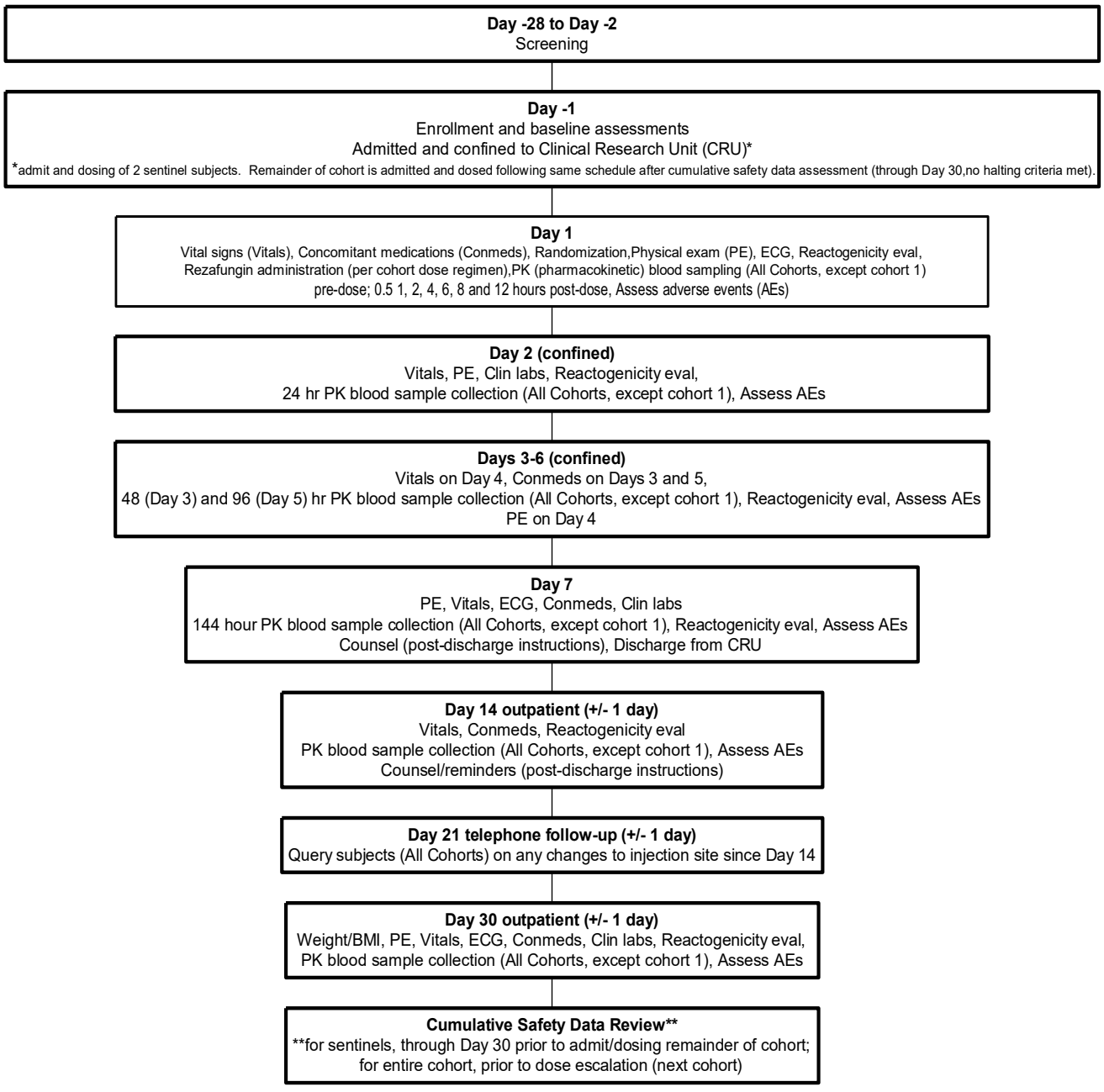


Figure 2

Study Schematic - MAD Study (Part 2) Cohorts 7, 8, 9, and10

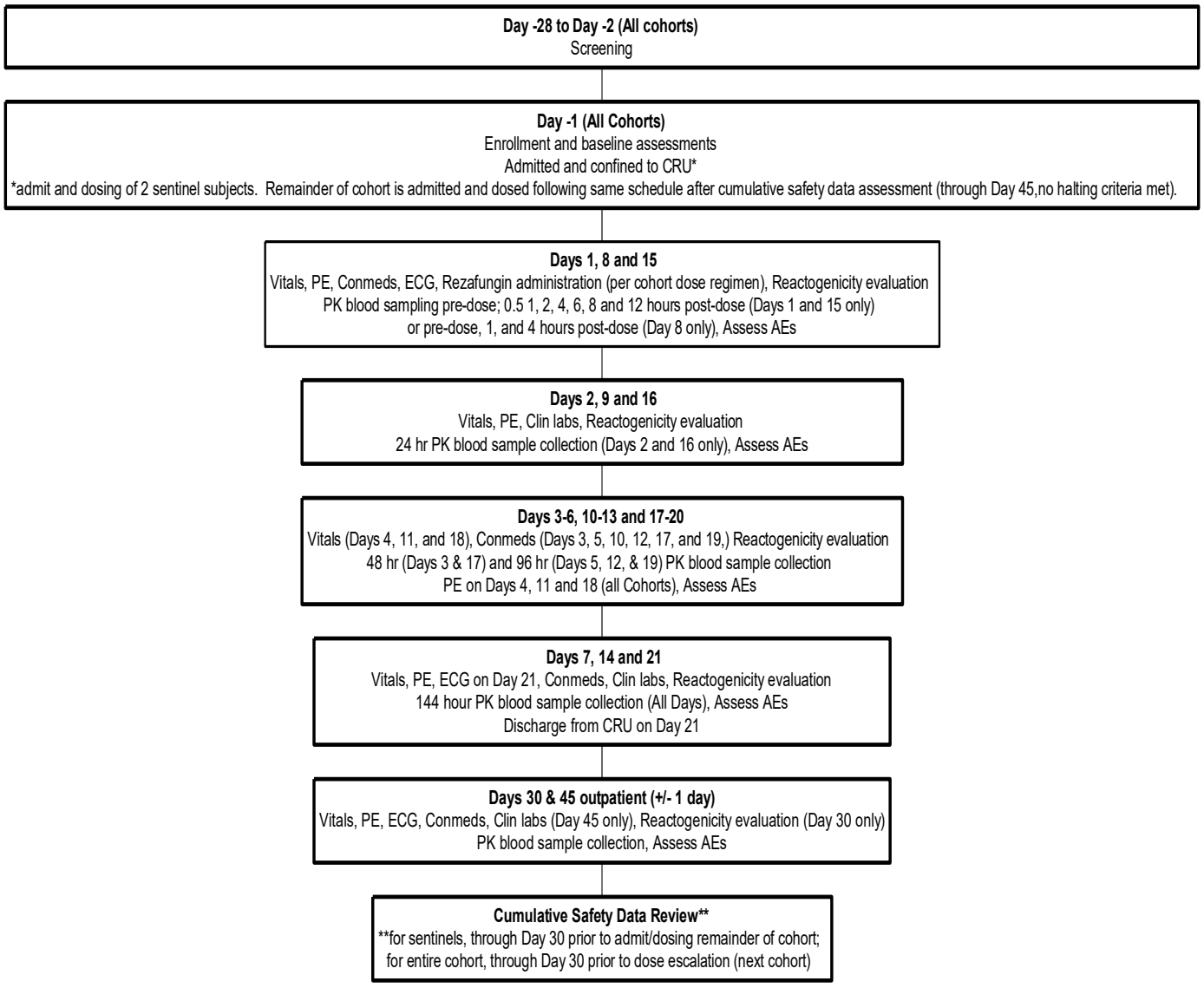
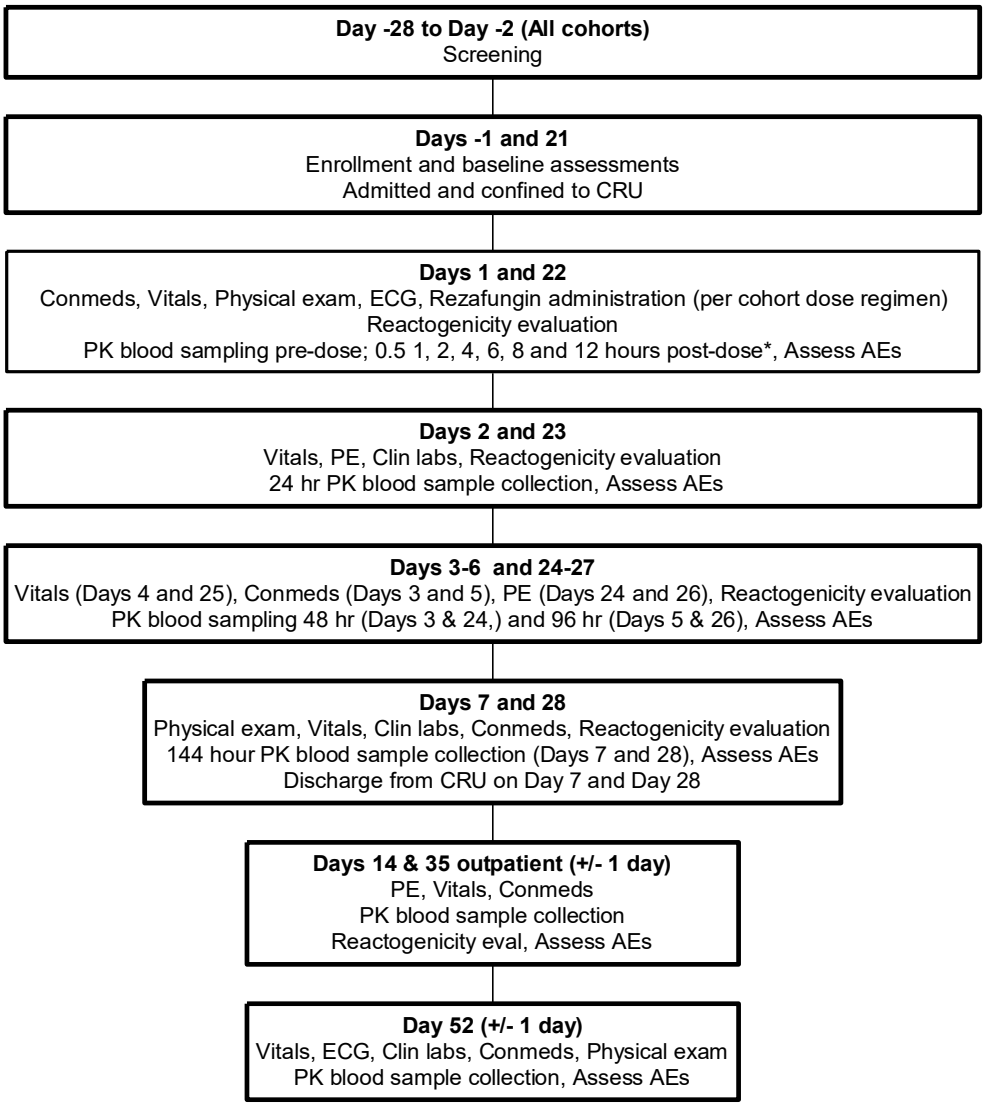


Figure 3

Study Schematic - Absolute BA Cross-over (Part 3) Cohort 11



*For IV portion, PK blood draws are timed from **start** of infusion.

1 KEY ROLES

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Contact information for additional key personnel is in the Manual of Procedures (MOP) for this trial.

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background

Immunocompromised patients, particularly those with hematological malignancies undergoing chemotherapy, and those undergoing hematopoietic stem cell transplant or solid organ transplant, are at risk for invasive fungal infections (IFIs) caused by *Pneumocystis*, *Candida*, *Aspergillus* and other fungal pathogens. These patients have impaired immune defenses against fungi owing to their underlying diseases and treatments.

Pneumocystis jirovecii causes lethal *Pneumocystis* pneumonia (PCP) in immunodeficient humans. Initially predominant among human immunodeficiency virus (HIV)+ individuals, PCP is now a public health concern for a broader population of immunosuppressed or otherwise immunodeficient patients, such as hematopoietic stem cell and solid organ transplant recipients; patients receiving cancer chemotherapy or biologic therapy, high-dose corticosteroids, immunotherapies, or anti-lymphocyte antibodies; patients with congenital immune deficiencies; and patients with autoimmune or chronic inflammatory disease[1,2].

PCP continues to be a problem worldwide even in the context of combined antiretroviral therapy in HIV+ patients[3]. The mortality rate of PCP remains unchanged at about 15% in HIV+ populations[2]. The rate in the developing world and certain urban areas of the US underserved by the healthcare establishment approaches 80%[4]. Recent evidence correlating *P. jirovecii* as a co-morbidity agent in respiratory conditions like chronic obstructive pulmonary disease[5], in association with anti-Tumor Necrosis Factor therapies[6], or with lung cancers[7] indicates a broadening of the PCP-susceptible population. Patients in these non-HIV+ categories fare worse than HIV+ patients. In a recent report, the mortality rate of non-HIV+ patients were 48% vs 17% in HIV+ patients[8]. A recent European estimate reported PCP incidence to be 1.5/100,000, with a fatality rate of 9.5%, lower than in past studies[1]. Though in support of previous evidence, lower mortality was observed in the HIV+ population (10-20%) compared with the non-HIV+ population (30-60%). Finally, productivity losses due to PCP have been calculated to be >$12 billion US dollars in 1999-2014[4].

The current standard for PCP treatment is trimethoprim/sulfamethoxazole (TMP/SMX), which is also highly effective and widely recommended for PCP prophylaxis. The efficacy of TMP/SMX, along with limited alternative options, has likely contributed to acceptance of its safety and tolerability issues. However, these issues are not minor and have a significant clinical impact on the use of TMP/SMX for prophylaxis with adverse effects reported in more than half of cases,

and treatment-limiting toxicities occurring in up to one-third of cases. Potential side effects include myelosuppression, renal failure, liver dysfunction, and hyperkalemia; in some cases, side effects require permanent discontinuation of TMP/SMX. Additional agents in use include atovaquone, dapsone, and inhaled pentamidine, which are considered second- or third- line to TMP/SMX based on reduced relative efficacy and cause treatment-limiting adverse effects[5]. In addition, resistance to TMP/SMX has been reported and may impact the efficacy of this first-line therapy and prophylaxis[9]. Rezafungin was highly effective in preventing *Pneumocystis* infections through inhibition asci (cyst) forms in a 6-week immunosuppressed mouse model for PCP prophylaxis[10]. In this model, prophylaxis was equivalent to TMP/SMX at lower and/or less frequent doses than required for *Candida*.

These safety/tolerability and resistance concerns may be a limiting factor to effective PCP prophylaxis. In addition to challenges to compliance, there is a lack of consensus on the appropriate duration of prophylaxis and longer durations, though warranted, may be difficult to implement with current agents. For example, in the context of transplantation, where practices vary by institution, transplant type, and individual immunosuppression risk, some patients may be recommended for lifetime prophylaxis[2,5].

Furthermore, evidence regarding the incidence and risks of late-onset PCP (> 1-year post-transplant) suggest a need for efficacious agents that can be tolerated in long-term prophylaxis[6,7,11].

The majority of IFIs in transplant and hematology are caused by *Candida* and *Aspergillus* species. Fluconazole, posaconazole, and micafungin are approved by the US FDA for the prevention of IFIs among HCT patients. Posaconazole is additionally approved for antifungal prophylaxis in those with hematological malignancies at least 13 years of age with prolonged neutropenia from chemotherapy. While the azoles are far more utilized for IFI prophylaxis and are better studies for this indication, these drugs are metabolized by cytochrome P450 isoenzymes, leading to the potential for serious drug interactions with concomitant administration of certain chemotherapeutic agents (including cyclophosphamide, vincristine, and thymidine kinase (TK) inhibitors or other immunosuppressants (including cyclosporine, tacrolimus and sirolimus). QT prolongation may be a limiting factor for patients on multiple medications. Administration of oral posaconazole in particular can be challenging in the presence of mucositis that prevents administration of food or nutritional supplements required for optimal posaconazole absorption. Discontinuations due to mucositis and colitis limit the utility of posaconazole prophylaxis. In a single-center, prospective study of patients with AML or after HCT taking posaconazole tablets, 80.5% of samples showed a concentration of at least

700 ng/mL at steady state, but 16% of patients stopped posaconazole prematurely owing to colitis, transaminase elevations and mucositis[12].

Voriconazole demonstrates wider inter-patient variability in serum concentrations that is due in part to variant CYP2C19 alleles. Individuals who are CYP2C19 ultra-rapid metabolizers have decreased voriconazole through concentrations, whereas poor metabolizers have increased through concentrations and are at increased risk of adverse experiences. Up to one-third of HCT recipients develop biochemical hepatotoxicity while on voriconazole that often leads to discontinuation of voriconazole by the clinicians regardless of causality. A long-term safety concern is the association of prolonged exposure to voriconazole with the development of non-melanoma skin cancers in HCT recipients. Use of amphotericin B (AmB) and its lipid derivatives for prophylaxis is problematic due to infusion and renal toxicities, as well as insufficient evidence regarding their efficacy in prophylaxis[12].

Echinocandins are the only class of antifungal agents at present that exerts activity on the fungal cell wall and not the cell membrane, resulting in no cross-reactivity with mammalian cell functions and thus reducing toxicity. Unlikely the azoles, echinocandins have significant fungicidal activity against *Candida* species and are currently recommended as first-line therapy for the treatment of candidemia. The echinocandins are generally very well tolerated with few adverse events (AEs) or drug interactions requiring discontinuation of the drug. Compared with the triazoles, the echinocandins had less than half the likelihood of discontinuation of therapy due to AEs. All the drugs in this class, caspofungin, micafungin, and anidulafungin, have a similar tolerability profile. The most common AE is injection site pain or phlebitis, occurring in up to 25% of patients receiving caspofungin, but in < 1% with anidulafungin[13].

2.2 Scientific Rationale

2.2.1 Purpose of Study

Rezafungin is an investigational echinocandin with many of the favorable efficacy and safety profiles of its echinocandin class. As with other echinocandins, rezafungin has excellent activity against *Candida*, *Aspergillus*, dermatophytes, and even some less common fungal infections such as *Talaromyces* (formerly *Penicilliosis*) *marneffei*, which has a substantial mortality in HIV+ people in Southeast Asia. Additionally, rezafungin possesses unique attributes. Its efficacy against PCP, pharmacokinetic (PK) behavior, and stability/solubility are of particular importance to the current context. In a study, rezafungin was highly effective in preventing *Pneumocystis* infections through inhibition asci (cyst) forms in a 6-week immunosuppressed mouse model for

PCP prophylaxis[10]. The prolonged half-life of rezafungin allows for once-weekly (or longer) dosing[14], and its stability/solubility enables subcutaneous (SC) formulation[15] that had moderate to high BA in rats and monkeys (up to ~80%). The smaller dose requirement also supports the possibility of SC dosing volume, as it would require smaller volumes to be administered. Safety advantages of rezafungin compared with TMP/SMX include lack of myelosuppression, low/no risk of drug-drug interactions, and no risk of sulfa allergy. Additionally, rezafungin appears to have safety advantages compared to second-line PCP agents, azoles and AmB, which are often poorly tolerated. Currently marketed echinocandins are dosed IV once-daily and are therefore not practical for prolonged or outpatient prophylaxis. Based on these preliminary factors, further trial is warranted to explore the potential of rezafungin as antifungal prophylaxis as a once-weekly IV or SC formulation.

2.2.2 Study Population

Up to 86 subjects aged 18-45 (inclusive) who are in good health and meet all eligibility criteria will be enrolled in the study. The demographics in the local population should ensure that male, female, and minorities (African American, Native American, Asian, and Hispanics) will be represented in the enrolled population. Subjects will be recruited using IRB-approved advertising/web site listing of the essential inclusion and exclusion criteria. Subjects will self-schedule online for a screening appointment based on their desire to participate and their evaluation of their suitability based on inclusion/exclusion criteria. Children, pregnant or breast-feeding women, prisoners, and other vulnerable populations will not be enrolled. See Section 9.4.

Neither women nor minorities will be excluded from participation in this study. Women of child-bearing potential may be included as per the inclusion criteria (Section 5.1). Subjects will be recruited without regard to gender or race. It is expected that race will reflect that within the community.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

This is the first study in humans using rezafungin via the SC route. The drug has been administered IV in multiple clinical trials. Risks of IV rezafungin exposure include possible histamine release reactions, including chest discomfort and flushing, as well as nausea and myalgia. The majority of events were mild, and all were transient.

Additionally, 71 participants with candidemia or invasive candidiasis were treated with rezafungin. The most commonly reported side effects for rezafungin were:

- Decreases in potassium in the blood, which may cause muscle cramps, constipation, weakness, and abnormal heart rhythms, especially in people with heart disease. This can cause you to feel lightheaded or faint. A very low potassium level can even cause your heart to stop.
- Diarrhea
- Nausea
- Anemia

One serious side effect that was possibly related to the study drug was reported in this study, the side effect was a delay in the timing of the way the heart normally beats and resolved without treatment.

In the group of participants with candidemia or invasive candidiasis, one participant in the rezafungin group had a side effect of sunburn (dosing group 400 mg on Day 1 and Day 8, with optional dosing on Days 15 and 21) following substantial sun exposure (photosensitivity). There were two side effects (reported in 2.8% of participants) that may represent tremor or nerve injury causing numbness or weakness: intensive care unit acquired weakness (reported as moderate intensity), and tremor (reported as mild intensity). These events of tremor/neuropathy that were potentially related to rezafungin were followed until resolution and both resolved

Echinocandins are typically well tolerated (Eraxis [anidulafungin] Prescribing information, 2013; Mycamine [micafungin sodium] Prescribing Information, 2013; Cancidas [caspofungin acetate] Prescribing Information, 2014). Potential drug class effects include risk of abnormal liver function tests, hepatitis, and hepatic failure. General and administration site events (infusion related reactions, peripheral edema, rigors, infusion site inflammation, and pyrexia) have been reported for echinocandins (Eraxis [anidulafungin] Prescribing Information, 2013; Mycamine [micafungin sodium] Prescribing Information, 2013; Cancidas [caspofungin acetate] Prescribing Information, 2014). Possible histamine-mediated symptoms have been reported in patients who received rapid infusions of echinocandins, including rash, urticarial, flushing, pruritus, dyspnea, hypotension, facial swelling, and vasodilation. Anaphylactic-like reactions have been reported with micafungin (Mycamine [micafungin sodium] Prescribing Information, 2013).

Due to preliminary results from a nonclinical phototoxicity study in rats (positive response to *in vitro* UV absorption), subjects should be advised to avoid sun exposure and any other type of

ultraviolet radiation (including tanning beds) without adequate protection. Investigators should report any AE potentially related to phototoxicity to the Sponsor.

Based on a fertility study in male rats, there is the potential risk for decreased sperm motility, increased incidences of abnormal sperm morphology, and testicular seminiferous tubular epithelial degeneration. These findings were noted at 2.5-fold the exposure expected at the highest dose in this study. The risk to humans is unknown, thus the male contraception requirements in inclusion criteria (see numbers 4 and 5 in Section 5.1.1) prohibit unprotected sexual intercourse and sperm donation within the study period and for 90 days thereafter (a total of 120 days from the last dose of study drug). This risk will be included in the ICF.

In a 3-month study in monkeys, there were observations of tremors, intention tremors, and histology consistent with axonal degeneration (potentially consistent with clinical presentation of neuropathy) first appearing at Week 6 of dosing. Dose-related microscopic findings of Schwann cell phospholipidosis were observed in the ganglia (≥3 mg/kg) and peripheral nerves (≥30 mg/kg) and dose-related Schwann cell hyperplasia was observed in the ganglia at ≥30 mg/kg; hyperplasia partially reversed but phospholipidosis was still present at the end of a 4-week recovery period. Tremoring reversed after 1 month of recovery but Schwann cell phospholipidosis was still present at the end of a 3-month recovery period. These observations occurred at 11.4-fold the maximum intended dose in this study. Given the high nonclinical exposure, relative to the current dose levels and expected exposure, the risk to study subjects is assessed as low. At the highest dose (about 20 times greater than the proposed human dose), severe neurobehavioral effects were observed. These effects were not seen in the levels at 11.4 times the maximum exposure proposed for humans.

Potential risks include temporary physical discomfort and emotional stress due to the nature of the evaluations and specimen collection procedures in this trial. Subcutaneous drug exposure may also be associated with pain and irritation at the injection site, risk of nodules, thickening and open sores at the injection sites; as seen in the cynomolgus monkey study. There was partial recovery of the sores after 4 weeks at the 120 mg/kg dosing level. The risks associated with insertion of the indwelling catheter and frequent blood draws are fainting, pain, bruising, and scarring. The catheter may pose a risk for clotting and infection. These risks are discussed with the subject during the consent process.

2.3.2 Potential Benefits

There are no known benefits to subjects participating in this trial. The knowledge gained in this trial may help society, especially those requiring treatment or prophylaxis of invasive fungal infections.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

3.1 Study Design Description

This is a Phase 1, single-center, three-part, prospective, randomized, double-blind trial of single- and multiple-ascending doses of rezafungin administered by SC injection to healthy adult subjects and a two-period crossover bioavailability study with two dosing sequences of rezafungin administered by SC → IV or IV → SC doses to healthy adult subjects.

3.1.1 Dosing Scheme and Duration of Study

3.1.1.1 Part 1 (SAD)

In Part 1 of this trial, 44 subjects will be split into six cohorts – one cohort of 4 subjects (3 rezafungin, 1 placebo) and five cohorts of 8 subjects each (6 rezafungin, 2 placebo) – will be randomized to receive single SC doses of rezafungin or placebo with dose escalation separated by a minimum of 4 weeks. Single-dose levels of rezafungin to be assessed will follow an ascending single-dose regimen in all except Cohort 1. The 1, 10, 30, 60, and 100 mg doses will be administered as 0.1 – 1.0 mL SC injections (abdomen) and the 200 mg dose as 2 x 1 mL injections (in same abdominal quadrant). A schematic of the SAD study design is shown in (Table 1). Administration details are included in the protocol-specific Manual of Procedures (MOP) to this study.

Table 1: Design for SC Dosing in SAD (Study Part 1)

Cohort	Dose (mg)	Dose Volume (mL)	Number of Doses	Number of Subjects*	
				Rezafungin SC Injection	Placebo
1	**1**	**0.1****	**1**	**3**	**1**
2	10	0.1	1	6	2
3	30	0.3	1	6	2
4	60	0.6	1	6	2
5	100	1	1	6	2
6	200	1 (in each of 2 injections) ***	1	6	2
Total Number of Subjects				33	11
				44	

*Within each cohort two sentinel subjects will be admitted initially, and the randomization scheme will be designed to ensure that one subject will receive rezafungin and the other will receive placebo. All sentinel subject safety data through Day 30 will be reviewed by the PI prior to dosing the remainder of cohort. Safety data for each cohort through Day 30 will be confirmed by review of objective pre-defined criteria before continuing to the next cohort.
**In order to administer this dose, the drug product solution from the SC drug product vial (Rezafungin Injection, for subcutaneous use, 100 mg/mL) will be diluted 1:10 in 5% Dextrose Injection, USP. Then 0.1 mL of the diluted solution will be administered. Details are included in the MOP for this study.
***The 200 mg (2 x 1 mL) SC dose will be injected as 1 mL each in the same abdominal quadrant, separated by approximately 5 cm. Details are included in the MOP for this study.

3.1.1.2 Part 2 (MAD)

The first cohort for Part 2 of this trial (Cohort 7) can begin after the FDA has reviewed and assessed the SAD safety and PK data and providing no halting criteria have been met. In Part 2, subjects in four cohorts of 8 subjects each (6 rezafungin, 2 placebo) will be randomized to receive SC doses of rezafungin or placebo on Days 1, 8, and 15 of the MAD portion of the study. Dose levels of rezafungin to be assessed will follow an ascending multiple-dose regimen (30 mg x 3 doses, 60 mg x 3 doses, 100 mg x 3 doses, and 200 mg x 3 doses). A schematic of the MAD study design is shown in (Table 2).

Table 2: Design for SC Dosing in MAD (Study Part 2)

Cohort	Dose (mg)	Dose Volume (mL)	Number of Doses	Number of Subjects*	
				Rezafungin SC Injection	Placebo
7	30	0.3	3	6	2
8	60	0.6	3	6	2
9	100	1	3	6	2
10	200	1 (in each of 2 injections)**	3	6	2
Total Number of Subjects				24	8
				32	

*Within each cohort two sentinel subjects will be admitted initially, and the randomization scheme will be designed to ensure that one subject will receive rezafungin and the other will receive placebo. All sentinel subject safety data through Day 30 will be reviewed by the PI prior to dosing the remainder of cohort. Safety data for each cohort through Day 30 will be confirmed by review of objective pre-defined criteria before continuing to the next cohort.
**The 200 mg (2 x 1 mL) SC dose will be injected as 1 mL each in the same abdominal quadrant, separated by approximately 5 cm. Each dose will be administered in a different quadrant (total 3 quadrants). Details are included in the MOP for this study.

3.1.1.3 Part 3 (BA)

Part 3 of this study may be run in parallel with Cohort 7 of the Part 2 (MAD) portion of this study, upon completion of safety data review for all Cohorts 1-6 of Part 1 (SAD). In the unblinded Part 3 cross-over portion of this trial, 10 subjects will be randomized to one of two sequences of 5 subjects each to receive a SC→IV or IV→SC sequence of study drug administration. In sequence 1 (SC→IV), rezafungin (100 mg or MTD in Part 1) administered by SC injection on Day 1 followed by rezafungin (100 mg or MTD in Part 1) administered by IV infusion over 60 minutes on Day 22; or in Sequence 2 (IV→SC), rezafungin (100 mg or the maximum tolerated dose in Part 1) administered by IV infusion over 60 minutes on Day 1 followed by rezafungin (100 mg or the maximum tolerated dose in Part 1) administered by SC injection on Day 22. Maximum tolerated dose (MTD) is defined as the highest dose level with no withdrawals by subject or investigator due to AEs related to study product for Part 1 (SAD) Cohorts 1-6. A schematic of the BA study design is shown in Table 3.

Table 3: Design for SC Dosing in Absolute BA Cohort (Study Part 3)

Sequence		Day 1 (Period 1) Dose/Volume/Route	Day 22 (Period 2) Dose/Volume/Route	Number of Subjects*
1 (SC → IV)		100 mg x 1 mL SC injection	100 mg 250 mL IV infusion	5
2 (IV → SC)		100 mg 250 mL IV infusion	100 mg 1 mL SC injection	5
	Total Number of Subjects			10

*Part 3 may be run following the cohort dosed at the same dose level (100 mg or MTD) in Part 1 (SAD).

The BA of the SC dose compared to the IV dose will be determined as the ratio of the rezafungin area under the plasma concentration versus time curve (AUC) values from each administration.

3.1.2 Rationale for Starting Dose

In the single-dose cynomolgus monkey trial (NC101), SC rezafungin 30 mg/kg (1 mL per injection of 100 mg/mL solution) was well tolerated with minor non-adverse skin findings ranging from very slight to slight erythema, and very slight to moderate edema. A multiple dose cynomolgus monkey trial (NC107), at doses of 30, 60, and 120 mg/kg (given as 1 mL per injection of 100 mg/mL solution in 1, 2, or 4 injections/animal every 3 days, respectively) was not tolerated, with all dose groups having adverse toxicity at the injection sites. Inflammation ranged from minimal to severe, with moderate severity and higher grades resulting in clinical and macroscopic observations of nodules, thickening, and in the most severe cases, open sores at the injection sites. At the low adverse effect level of 30 mg/kg, adverse observable skin lesions were first observed from Day 11 to 14 and were generally associated with the 4th (Day 9) injection (4-6 animals). One lesion was observed on Day 12 at the site of the 2nd (Day 3) injection, and one animal had no lesions. These findings reversed following 4 weeks of recovery at the low- and mid-dose levels and in all but one animal at the high-dose level. A suitable starting dose was selected per *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*[16]. This guidance recommends that if local toxicities are dose limiting the "therapeutics should be normalized to concentration (e.g., mg/area of application) or amount of drug (mg) at the application sites".

In the NHP study, cynomolgus monkeys weighing approximately 3 kg were dosed multiple times with 30 mg/kg, or 90 mg of rezafungin.

As shown in Table 4, the SAD escalation will begin with a lower starting dose and propose an initial single-dose cohort of 1 mg/injection, which would represent roughly an hundred-fold safety margin (by total absolute dose) from the 30 mg/kg dose cohort used in both the single dose subcutaneous toxicology study (NC-101) and the lowest dose tested from the repeat dose toxicology study (NC-107).

Table 4: Proposed Starting Dose Level in the Clinic

mg	mg/kg dose	Volume	mL/kg
Cynomolgus Monkey (~3 kg)			
100	30	1 mL	0.33
200	60	2 mL*	0.67
400	120	4 mL*	1
Human (~70 kg)			
1	0.0143	0.10 mL	0.0014

*Given as multiple 1-mL injections

3.1.3 Dose Escalations

In Part 1/SAD, the initial cohort of 4 subjects will be administered 1 mg of rezafungin (3 subjects) or placebo (1 subject) as a single SC injection.

Dose escalation to each successive cohort during Part 1 will occur if none of the predefined dose escalation halting criteria are met through Day 30 (final visit). The FDA will review all safety and PK data from the SAD (Part 1) and determine if the study may proceed to the MAD (Part 2) and BA (Part 3) portions. Rezafungin doses for the MAD and BA portions will be determined after FDA review of the SAD data. Dose escalation during Part 2 will occur if none of the predefined dose escalation halting criteria are met through Day 30 after the first dose. This will be communicated through the following process:

1. An email from the site to the SDCC attesting that all data entry has been completed after the last subject has had their Day 30 visit, then data cleaning, as applicable, prior to the SDCC being able to generate the report.
2. A halting criteria report will be provided by the SDCC to DMID.
3. If based on the entered data in EDC, none of the escalation criterion is met, then the SDCC will open the database for the following cohort after confirmation from DMID that the study may proceed to the next cohort.
4. If any of the criterion is met, the SDCC will provide the dose escalation report and an ad-hoc SMC meeting will be convened to seek recommendation from the SMC.

Part 2 (MAD) and Part 3 (BA) may not begin until after FDA has reviewed all safety and PK data from Part 1 (SAD) and given agreement that it is safe to proceed. The doses for Parts 2 and 3 may be updated after FDA review of the SAD data. There will be a scheduled SMC data review meeting prior to start of Part 2 (MAD) Cohort 7.

In order to efficiently identify the optimal therapeutic doses for use in future clinical trials, a flexible scheme of dose escalation, (based on ongoing study data) will be used that allows intermediate doses higher or lower than the planned doses (30, 60, 100, and 200 mg), upon protocol amendment and with IRB approval. However, no cohort will be dosed higher than the 200 mg free base equivalent.

Cohorts 2-6 in the SAD and all MAD cohorts will be conducted with sentinel dosing of rezafungin (i.e., dosing in 2 subjects followed by remaining six subjects). The randomization scheme will be designed to ensure that 1 subject will receive rezafungin and the other will receive placebo in sentinel dosing. The dosing of the remaining six subjects in the same cohort will not be initiated until a minimum of 4 weeks after the second sentinel dosing, and no serious adverse events (SAEs)/adverse events (AEs) have occurred that meet the predefined objective halting criteria for sentinels. The blinded safety and clinical laboratory data from all subjects in the cohort will be reviewed and confirm that none of the dose-escalation halting rules have been met before moving to the next higher dose cohort. If any of the predefined halting criteria is met, the study enrollment and dosing will be stopped until the SMC provides recommendations regarding continuation of the study (See Section 8.2.3).

3.2 Study Objectives

3.2.1 Primary

- To determine the safety and tolerability of single-ascending SC doses (SAD) of rezafungin.
- To determine the safety and tolerability of multiple-ascending SC doses (MAD) of rezafungin.
- To determine the pharmacokinetic (PK) profile in plasma of rezafungin in healthy adult subjects;

3.2.2 Secondary

To evaluate the bioavailability (BA) of rezafungin when administered by SC injection relative to IV infusion in healthy adult subjects.

3.3 Study Endpoints or Outcome Measures

3.3.1 Primary

- Safety and tolerability will be evaluated for single-ascending SC doses (SAD) of rezafungin. Safety will be assessed by adverse events and SAEs from start of dosing to Day 30, clinical laboratory tests at baseline and from Day 2 to Day 30, ECGs at Screening and post-dose on Days 1, 7, and 30, physical exams at baseline and post-dose on Day 1 to Day 30, vital signs at baseline and from Day 1 to Day 30, and injection site evaluation from dosing to Day 30. Tolerability will be assessed by occurrence of solicited local reactogenicity (injection site evaluation) from dosing to Day 30.

- Safety will be evaluated for multiple-ascending SC doses (MAD) of rezafungin. Safety will be assessed by adverse events and SAEs from start of dosing to Day 45, clinical laboratory tests at baseline and from Day 2 to Day 45, ECGs at Screening and post-dose on Days 1, 8, 15, 21, 30, and 45, physical exams at baseline to Day 45, and vital signs at baseline to Day 45. Tolerability will be assessed by occurrence of solicited local reactogenicity (injection site evaluation) from first dose to Day 45.

- Pharmacokinetic (PK) profiles of rezafungin will be assessed by measurement of drug levels in plasma after SC administration in each cohort (except for SAD Cohort 1). Plasma for PK analysis will be collected at planned timepoints up to Day 30 in the SAD cohorts, and Day 45 in the MAD cohorts. PK parameters will be estimated from the rezafungin plasma concentration-time data.

3.3.2 Secondary

The BA of rezafungin when administered by SC injection relative to IV infusion will be assessed by measurement of drug levels in plasma after administration by SC injection or by IV infusion in each cross over period. Plasma samples will be collected at planned timepoints up to Day 52 for Part 3/BA The absolute BA will be calculated as the ratio of AUC for the SC injection and AUC for the IV infusion of administration.

4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

4.1 Study Product Description

The active ingredient, rezafungin acetate, a cyclic hexapeptide, is a semi-synthetic echinocandin synthesized from a fermentation product of *Aspergillus nidulans*. Two formulations will be used for the study, one for SC administration and one for IV administration.

Subcutaneous (SC) formulation: Rezafungin Injection, for Subcutaneous Use, 100 mg/mL, is a sterile liquid product supplied as a colorless to pale yellow liquid in single-dose vials containing 1.0 mL of extractable volume. The active pharmaceutical ingredient is rezafungin acetate, a water-soluble amorphous acetate salt. The inactive ingredient is mannitol.

Intravenous (IV) formulation: Rezafungin for Injection, 200 mg/vial, is a sterile product supplied as a white to pale yellow lyophilized powder in single-dose glass vials for reconstitution with Sterile Water for Injection, United States Pharmacopeia (USP). The reconstituted product is diluted in 0.9% Sodium Chloride Injection, USP for IV infusion. The active pharmaceutical ingredient is rezafungin acetate, a water-soluble amorphous acetate salt. The inactive ingredients include excipients of mannitol, polysorbate 80, and histidine.

Placebo is 5% Dextrose Injection, USP, a sterile, nonpyrogenic solution of dextrose in water for injection. The solution has the osmolarity of 252 mOsmol/L, which is slightly hypotonic. This solution contains no bacteriostat, antimicrobial agent or added buffer.

Reconstitution solution is Sterile Water for Injection, (WFI), USP, which is a clear, colorless solution.

4.1.1 Formulation, Packaging, and Labeling

Subcutaneous Formulation: Rezafungin Injection, for Subcutaneous Use, 100 mg/mL

Rezafungin Injection is a sterile liquid product supplied in single-dose 2 mL vials containing 100 mg of rezafungin in 1.0 mL of extractable volume. The active pharmaceutical ingredient is rezafungin acetate, a water-soluble acetate salt. The inactive ingredient is mannitol.

For SC administration for Parts 1, 2, and 3 of the study, the appropriate volume of solution is withdrawn via syringe for administration to the subject for doses of 10 mg and up. To administer

a 1 mg dose, the solution from the product vial (Rezafungin Injection, for Subcutaneous use, 100 mg/mL) is diluted 1:10 in 5% Dextrose Injection, USP, then 0.1 mL of the diluted solution is injected. Further details are provided in the protocol-specific MOP.

Rezafungin Injection, for Subcutaneous Use, 100 mg/mL, will be labelled according to manufacturer or regulatory specifications and will include the statement "Caution: New Drug – Limited by Federal Law to Investigational Use".

IV Formulation: Rezafungin for Injection, 200 mg/vial

The IV formulation will be used for Part 3 of the study.

Rezafungin for Injection, 200 mg/vial, is supplied as a white-to-pale-yellow lyophilized powder (200 mg/vial) in single-dose 20 mL glass vials for reconstitution with Sterile Water for Injection, USP. The reconstituted product is a clear, colorless to pale yellow solution free of visible particulate. The reconstituted product is diluted in 250 mL of normal saline and administered by IV infusion. Further details are provided in the protocol-specific Manual of MOP.

The active pharmaceutical ingredient is rezafungin acetate, a water-soluble acetate salt. The inactive ingredients include excipients of mannitol, polysorbate 80, and histidine.

Rezafungin for Injection, 200 mg/vial, will be labelled according to manufacturer or regulatory specifications and will include the statement "Caution: New Drug – Limited by Federal Law to Investigational Use".

Placebo (5% Dextrose Injection, USP)

5% Dextrose Injection, USP solution is sterile and nonpyrogenic. It is a parenteral solution containing dextrose in water for injection intended for intravenous administration. Each 100 mL of 5% Dextrose Injection, USP, contains dextrose monohydrate, 5 g in water for injection. The caloric value is 170 kcal/L. The osmolarity is 252 mOsmol/L (calc.), which is slightly hypotonic. The solution pH is 4.3 (3.2 to 6.5).

WFI (Reconstitution Solution)

WFI is USP grade sterile water for injection that is nonpyrogenic and contains no bacteriostatic agent or added buffer.

4.1.2 Product Storage and Stability

Rezafungin Injection, for Subcutaneous Use, 100 mg/mL

Store at 2-8°C (36-46°F).

Rezafungin for Injection, 200 mg/vial
Store at 20-25°C (68-77°F) (See USP Controlled Room Temperature; excursions between 15°C and 30°C [59-86°F] are permitted).

Placebo (5% Dextrose Injection, USP)
Store at 20-25°C (68-77°F) (See USP Controlled Room Temperature). Protect from freezing.

WFI (Reconstitution Solution)
Store at 20-25°C (68-77°F) (See USP Controlled Room Temperature; excursions between 15°C and 30°C [59-86°F] are permitted). Protect from freezing.

4.2 Acquisition/Distribution

Rezafungin Injection, for Subcutaneous Use, 100 mg/mL and Rezafungin for Injection, 200 mg/vial
Rezafungin will be provided by Cidara Therapeutics, Inc. Upon request by Division of Microbiology and Infectious Diseases (DMID), it will be shipped to the following address:

DMID-Clinical Materials Services (CMS)
Fisher BioServices
20439 Seneca Meadows Parkway
Germantown, MD 20876
Tel: 240-477-1350
Email: DMID.CMS@thermofisher.com

Rezafungin will be shipped from DMID-CMS to the ICON Early Phase Services upon request and approval by DMID.

Placebo (5% Dextrose Injection, USP)
5% Dextrose Injection, USP will be supplied by ICON.

WFI (Reconstitution Solution)
WFI will be supplied by ICON.

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 Rezafungin for Injection – SC (100 mg/mL) and Rezafungin for Injection-IV (200 mg). Study product preparation will be performed by the site's unblinded research pharmacist on the same day of study drug administration.

Visually inspect all study products/diluent upon receipt and prior to use. If the study products/diluent appear to have been damaged, contaminated, or discolored, contain visible particulate matter, or if there are any concerns regarding its integrity, do NOT use the affected study products/diluent. The affected study products/diluent must be quarantined at the appropriate temperature and labeled 'Do Not Use' (until further notice). The Site Principal Investigator (PI) or responsible person should immediately contact the DMID Product Support Team (see MOP for contact information) and DMID Clinical Project Manager for further instructions before any additional study product administrations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study products/diluent can be used. If it cannot be used, the site will receive specific instructions on how to return the affected study products/diluent to the DMID CMS or destroy it on site. If the study products/diluent are unusable, study personnel will use another vial from the study supply. Replacement vials may be requested by contacting DMID. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

Two formulations will be used for the study.

Subcutaneous Formulation: Rezafungin Injection, for Subcutaneous Use, 100 mg/mL

An appropriate volume of solution is withdrawn from the vial via syringe and administered for doses of 10 mg and up. To administer a 1 mg dose, the solution from the product vial (Rezafungin Injection, for Subcutaneous use, 100 mg/mL) is diluted 1:10 in 5% Dextrose Injection, USP, then 0.1 mL of the diluted solution is injected. Refer to the MOP for further details.

IV Formulation: Rezafungin for Injection, 200 mg/vial

The lyophilized powder is first reconstituted with Sterile Water for Injection, USP, and then diluted with Normal Saline, 0.9% Sodium Chloride Injection, USP, 250 mL, for infusion. For detailed instructions on reconstitution and/or dilution, refer to the MOP for this study.

Placebo (5% Dextrose Injection, USP)
For placebo SC injection, the appropriate volume to match the volume to be administered in the active arm of the trial is withdrawn using a syringe.

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

The Site PI is responsible for the distribution and disposition of study drug and has ultimate responsibility for its accountability. As this is a blinded trial, the Site PI will delegate this responsibility to the unblinded Site Pharmacist. The Site Pharmacist will be responsible for maintaining complete records and documentation of study drug receipt, accountability, dispensation, temperature monitoring, storage conditions, and final disposition.

Study drugs, whether administered or not, will be documented on the appropriate study drug accountability record or dispensing log. Used and unused Rezafungin vials will be retained at temperature specified on the label until monitored and released for disposition as per DMID Requirements in the MOP. Any unused solution left in the IV infusion bag or IV tubing after administration to the subject will be discarded as biohazardous waste in accordance with local institutional policies. The infusion bag may be discarded prior to monitoring.

Upon completion of this trial and after the final monitoring visit, any remaining unused study drug will either be returned or destroyed appropriately at the clinical site as per sponsor requirements and instructions, or in accordance with disposition plans.

5 SELECTION OF SUBJECTS AND STUDY ENROLLMENT AND WITHDRAWAL

The inclusion/exclusion criteria for participation in this trial are listed below. All screening procedures must be completed during the screening period but may be performed on different days. Abnormal laboratory values may be confirmed at the PIs' discretion and one repeat value can be used to determine eligibility. Subjects cannot be re-screened if they do not meet eligibility criteria. Subjects who meet criteria but fall outside the screening window (i.e. subjects screened as alternative subjects and not selected on dosing day) may be rescreened a maximum of one time. Subjects may only be enrolled once into this trial.

No exemptions are granted on subject inclusion/exclusion criteria in DMID-sponsored studies. Questions about eligibility will be directed to the DMID Medical Officer.

5.1 Eligibility Criteria

5.1.1 Subject Inclusion Criteria

Subjects are eligible to enroll in this trial if they meet all the following criteria:

1) Males and females aged 18 to 45 years, inclusive.

2) Willing and able to provide written informed consent and authorization for use of protected health information;

3) Willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions (including confinement to the CRU) and is likely to complete the study as planned;

4) Males must be vasectomized or agree to use barrier contraception (condom with spermicide) from first dose of study drug until at least 18 weeks following the last dose of study drug.

5) Males must agree to refrain from sperm donation from first dose of IP through at least 18 weeks after last dose of investigational product (IP).

6) Females are eligible if they are of non-childbearing potential[3] or if they use a highly effective[4] method of contraception for 30 days prior to dosing and for a minimum of 30 days after dosing;

[3]Non-childbearing potential is defined as: Pre-menopausal with documentation of irreversible surgical sterilization (i.e., hysterectomy, bilateral oophorectomy, or bilateral salpingectomy (but not tubal ligation alone); or, Post-menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with FSH levels ≥40 mIU/mL at Screening.

[4]A highly effective contraceptive method is, defined by <1% failure rate that is not affected by user adherence, include surgical sterilization and long-acting reversible contraception (LARC). LARC comes in three forms: progestin-releasing subdermal implants (Nexplanon and Implanon [Merck]); copper intrauterine devices (IUD) (ParaGard [Teva]); and levonorgestrel-releasing IUDs (Mirena [Bayer], Skyla [Bayer], and Liletta [Allergan/Medicines360]. Subjects must use one of these three methods.

7) Subject is in good health as deemed by the Investigator.[1-2]

[1]Good health is defined by the absence of any medical condition described in the exclusion criteria in a subject who undergoes a medical history, with a normal complete physical examination including resting vital signs (heart rate of 51-60 bpm allowed, per PI discretion), and screening safety laboratory testing.

[2]If the subject has an active, ongoing medical condition, the condition cannot meet any of the following criteria: 1.) first diagnosed within 3 months of enrollment; 2.) is worsening in terms of clinical outcome in last 6 months; or 3.) involves need for medication that may pose a risk to subject's safety or significantly impede assessment of adverse events if they participate in the study.

8) Subjects with a body mass index (BMI) (weight in kg divided by height in m, squared) between 18.5 and/or 35.0 kg/m^2, inclusive, and a minimum weight of 50 kg;

9) Subjects must refrain from strenuous physical activity that could cause muscle aches or injury, including contact sports, at any time from screening until completion of the trial.

10) Subjects must refrain from over-the-counter and-prescription medications[1] and nutritional supplements within 14 days before first study drug administration, and until after the final study visit.

[1]except for hormonal contraceptives, acetaminophen or ibuprofen.

11) Subject has adequate venous access for blood collection.

5.1.2 Subject Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria:

1) History of any hypersensitivity or allergic reaction to echinocandins or excipients (mannitol, polysorbate 80, histidine) of the rezafungin for injection and rezafungin for infusion formulations.

2) Subjects presenting with a clinically significant condition;[5]

   [5]Subjects with any of the following must not be included into the study: clinically significant oncologic, infectious, cardiovascular, pulmonary, hepatic, gastrointestinal, hematologic, metabolic, endocrine, neurologic, immunologic, renal, psychiatric, or other condition that in the opinion of the Investigator would preclude the safe participation of the subject in the study or would prevent the subject from meeting the study requirements.

3) Any condition that in the opinion of the Investigator could significantly impact drug absorption, distribution, or elimination;

4) Symptoms of acute illness or chronic disease within 14 days of initial dosing;

5) Positive screen for hepatitis B virus surface antigen, hepatitis C virus antibody, or HIV antibody;

6) Subjects with clinical laboratory values outside the site reference ranges[1] prior to initial dosing;

   [1]Clinical laboratory values outside the site reference ranges, if considered by the site investigator to be clinically insignificant, are acceptable if not exceeding Grade 1 severity. One repeat of lab testing is allowed to make this determination during screening.

7) Abnormal ECGs. See Section 7.1 Clinical Evaluations for exceptions;

8) Female subject of childbearing potential who is pregnant,[6] lactating, or planning to become pregnant during the study period or at least 30 days after the final dose of study product;

   [6]Having a positive serum pregnancy test at the Screening Visit or any other specified time point prior to the dose of study product.

9) Received any prescription medications (except for hormonal contraceptives) within 14 days before first study drug administration;

10) Received any non-prescription medications, vitamins, herbal or dietary supplements[7] within 14 days of initial dosing, unless prior approval is granted by both the Investigator and the Sponsor;

[7]Excluded from this list is intermittent use of acetaminophen at doses of ≤2 g/day or ibuprofen ≤1200 mg/day. However, acetaminophen only is accepted to treat AEs for pain (i.e. headaches) during in-clinic stay.

11) Current smoker or tobacco[8] use within 90 days prior to screening or while a subject is enrolled in the study;

[8]Tobacco use includes vaping, smoking tobacco, the use of snuff and chewing tobacco, and other nicotine or nicotine- containing products

12) History of illicit/illegal drug use prior to dosing or while a subject is enrolled in the study[9] or reports an alcohol or substance abuse problem* within 6 months of dosing;

[9]A urine drug test will be performed at screening and upon admission to the CRU. Drug screen includes amphetamines, barbiturates, cocaine, opiates, cannabinoids, phencyclidine, and benzodiazepines.

*Inclusive of vaping of non-nicotine products

13) Consumed foods or beverages containing alcohol or xanthines/caffeine [a,b]:

a. Alcohol: ≤ 48 hours before the first study drug administration, until discharge;

b. Xanthines/caffeine: ≤ 24 hours before the first study drug administration, until discharge;

14) Received any live or killed vaccines or immunoglobulins within 14 days of dosing;

15) Donated blood or blood products or experienced significant blood loss within 60 days of dosing;

16) Received a blood transfusion within 14 days of dosing;

17) Previous participation in this trial, any other rezafungin trial, or any trial[10] within 28 days of dosing. Plans to enroll in another clinical trial[11];

[10] Includes trials that have a study intervention such as a drug, biologic, or device.

[11] Includes trials that could interfere with safety assessment of the investigational product at any time during the study period

18) The PI considers that the subject should not participate in the trial.

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 withdraw their consent at any time without penalty or loss of benefits to which they are otherwise entitled.

A Site PI may also withdraw a subject from the study or from receiving the study drug for any reason. Follow-Up safety evaluations will be conducted, if the subject agrees. If a subject withdraws or is withdrawn before completion of this trial, the reason(s) will be recorded in the electronic case report form (eCRF). In either case, the reason for withdrawal will be clearly documented and specifically if the reason for withdrawal was related to study drug intolerance or other adverse event.

The reason(s) for withdrawal from the study might include, but are not limited to, the following:

- Subject no longer meets eligibility criteria;
- subject meets individual halting criteria (listed in Section 8.7.3);
- subject becomes noncompliant;
- medical disease or condition or new clinical finding(s) for which continued participation, in the opinion of the Site PI, might compromise the subject's safety, interfere with the subject's successful completion of this trial, or interfere with the evaluation of responses;
- subject is lost to FU;
- determined by a physician's discretion to require additional therapy not indicated in the protocol to ensure subject's health and well-being. The reason(s) for discontinuation of the study drug might include, but are not limited to;
    - subject becomes pregnant;
    - determined by a physician's discretion to require additional therapy not indicated in the protocol to ensure subject's health and well-being.

The Site PI will be explicit regarding trial FU (e.g., safety FU) that might be carried out if the subject will not receive further study drug. If the subject consents, every attempt will be made to follow all AEs through resolution. The procedures that collect safety data for the purposes of research will be included in the original ICF or the Site PI may seek subsequent informed consent using an IRB/IEC-approved ICF with the revised procedures.

The Site PI will inform the subject that data already collected will be retained and analyzed even if the subject withdraws from this trial.

5.2.2 Handling of Withdrawals and Discontinuation of Administration

Subjects who sign and date the ICF but fail to be randomized will be defined as screen failures. Site personnel will maintain documentation for all subjects who sign an ICF.

Subjects will be informed that they have the right to discontinue study drug and/or withdraw from this trial at any time for any reason without prejudice to their medical care. If the subject has received the study drug, data collected for withdrawn subjects will be evaluated for safety and PK.

In all cases of withdrawal, the reason for withdrawal will be recorded. Subjects who receive any amount of study drug and who are discontinued from this trial will be asked to complete all FU safety assessments including FU of any AEs before termination from this trial.

5.2.3 Lost to Follow-Up

If subjects fail to appear for a FU assessment, extensive effort, (i.e., three 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 them, or at least to determine their health status. These efforts will be documented in the subjects' records.

5.2.4 Subject Replacement

Subjects who have not received any amount of study drug and discontinue their participation may be replaced.

Additionally, the first subject in each cohort to discontinue from participation due to loss to follow up, after receiving any amount of study product, is not replaced; if more than one subject in any cohort discontinues participation, these subjects will be replaced. Replacement of any subject is at the discretion of the PI in consultation with the Sponsor. Replacement subjects

should be allocated to the same treatment as the subject they replaced. The SDCC must be contacted prior to enrolling a replacement subject.

5.2.5 Study Termination

Although DMID has every intention of completing this trial, it reserves the right to terminate this trial at any time for clinical or administrative reasons.

If this trial is prematurely terminated by the Sponsor, any regulatory authority, or the Site PI for any reason, the Site PI will promptly inform the subjects and assure appropriate therapy or FU for the subjects, as necessary. The Site PI will provide a detailed written explanation of the termination to the IRB/IEC.

6 STUDY PROCEDURES

6.1 Recruitment

Up to 86 subjects aged 18-45 years (inclusive) who are in good health and meet all eligibility criteria will be enrolled in this trial. The demographics in the local population should ensure that male, females, and minorities (African American, Native American, Asian and Hispanics) will be represented in the enrolled population. Subjects will be recruited using IRB-approved advertising/web site listings of the essential inclusion and exclusion criteria. Subjects will self-schedule online for a screening appointment based on their desire to participate and their evaluation of their suitability based on inclusion/exclusion criteria. Children, pregnant or breast-feeding women, prisoners, and other vulnerable populations will not be enrolled.

Upon arrival to the Clinical Research Unit (CRU), individuals will be checked for eligibility through the Verified Clinical Trials (VCT) process (after signing the IRB-approved VCT ICF) and then given the IRB-approved ICF and HIPAA form, and be assigned to Part 1, 2 or 3 of the study for enrollment. After presentation of the ICF and individuals indicate their desire to proceed, they will be brought to a private room and given an opportunity to ask questions of the licensed nurse or doctor delegated to perform consenting. After the subject signs the ICF, protocol procedures will be initiated.

Trial retention strategies will include education and explanation of the trial schedule and procedures during Screening and Enrollment visits. In addition, reimbursements will be disbursed at specific timepoints during this trial with the amount contingent on completing trial procedures. Subjects will be reminded of visits ahead of time, and trial staff will contact subjects who miss appointments to encourage them to return for completion of safety evaluations.

6.2 Screening (Day -28 to Day -2) Parts 1-3 (All Cohorts)

After providing written informed consent, each subject will be assigned a subject identification number and undergo an eligibility assessment. The following will be done during the screening period (within 28 days before study drug administration). Results of screening tests and procedures will be evaluated by the Site PI to determine eligibility before enrollment and randomization.

- Record demographics including age, gender, race, and ethnicity. Obtain contact information.
- Obtain medical history that includes:
    a) current medical diagnoses,
    b) past medical diagnoses,
    c) hospitalizations,
    d) major surgical procedure,
    e) blood transfusions or immunoglobulin administrations within 14 days of dosing,
    f) live vaccines within14 days of dosing,
    g) killed vaccines within 14 days of dosing,
    h) blood or blood product donation, or significant blood loss within 60 days of dosing,
    i) allergic reactions,
    j) drug and/or alcohol use or dependence,
    k) receipt of an investigational drug within 28 days of dosing.
- Review concomitant medication history, including all medications taken within 14 days of dosing.
- Review recent menstrual history (female subjects only) and current use of contraceptive method.
- Perform complete PE by licensed clinician listed on Form FDA 1572.
- Obtain height and weight and calculate BMI.
- Take resting vital signs after being at rest for at least 5 minutes.

- Obtain fasting (at least 8 hours) blood samples for clinical chemistry, hematology, coagulation tests, serum pregnancy test [if female of childbearing potential], FSH [if female and post-menopausal], and serology screen (serum HIV, HBsAg, and HCV antibodies).
- Obtain urine sample for urinalysis, urine drug screen and urine alcohol.
- Obtain urine sample for cotinine test.
- Obtain a 12-lead ECG, after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period) to assess heart rate, rhythm, and interval information such as PR, QRS, QT, and QTc, after being supine for at least 5 minutes.
- Counsel on the avoidance of pregnancy for women of child-bearing potential and use of barrier contraception for men.
- Counsel on the avoidance of vaccines, blood/blood product/sperm donation and drugs and dietary restrictions listed in Section 5.1.

6.3 Admission to the CRU (Day -1) Parts 1 and 2 (All Cohorts) and Part 3 (Cohort 11) Days -1 and 21

Subjects will be admitted to the CRU on the day before injection (or infusion for Part 3) and the following procedures will be performed:

- On admission to the CRU on Day-1, review inclusion/exclusion criteria to ensure the subject is eligible for enrollment. For Part 3, Day 21, review inclusion criteria numbers 2-7 and 10-11, and exclusion criteria numbers 2-4 and 8-18 (from Section 5.1.2) to ensure the subject remains eligible for dosing.
- Update medical history.
- Review and update concomitant medications.
- Perform targeted PE.

- Obtain resting vital signs after being at rest for at least 5 minutes.
- Obtain weight, calculate BMI.
- Obtain blood samples for baseline fasting (at least 8 hours) clinical chemistry, hematology, coagulation tests, serum pregnancy test [if female of childbearing potential]); for the Day -1 visit, if clinical chemistry, hematology or coagulation test result(s) are outside of the reference range(s), they may not be repeated; if a result is not considered by the site investigator to be clinically insignificant, the subject is removed from the study.
- For women of child-bearing potential, perform a serum pregnancy test (results must be confirmed negative before dosing).
- Obtain blood and urine samples for safety clinical labs.
- Obtain urine sample for drug screen and urine alcohol.
- Obtain urine sample for cotinine test.
- Part 3 (Cohort 11) only, Day 21 – review Memory Aid.

6.4 Part 1 (Cohorts 1 through 6)

6.4.1 Day 1 – Inpatient CRU

- On the morning of Day 1, study drug or placebo will be administered via SC injection in the abdomen at a slow steady pace. Subjects will be inpatients in the CRU and will undergo the following procedures, which are listed in the Schedule of Study Procedures and Evaluations (Appendix A) and detailed in Clinical Evaluations (Section 7).
- Randomize the subject.
- Obtain vital signs before study drug dosing (within 60 minutes of study drug dosing) after resting in a supine or semi-supine position for at least 5 minutes. This is to be documented as the Baseline prior to dosing.
- Perform targeted PE.

- Obtain a 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period) and within 60 minutes before study drug dosing.
- Baseline skin assessment at SC injection site area prior to study drug dosing (see Section 7.1.3 and MOP for this study).
- Administer study drug.
- Obtain vital signs at 15 minutes (±5 min), 1 hour (±10 min), and 2 hours (±10 min) after dosing, after resting in a supine or semi-supine position for at least 5 minutes.
- Collect PK blood samples for pre-dose, (collected within 60 minutes before study drug dosing) and at 0.5 h (±5 min), 1 h (±10 min), 2 h (±10 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), and 12 h (±10 min). No PK blood samples collected in Cohort 1.
- Assess reactogenicity at SC injection site(s) at 1 h (±10 min) and 4 h (±10 min) post-dose (see Section 7.1.3 and MOP for this study).
- 12-lead ECG at 4 hours (±10 minutes) after injection after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.
- Issue Memory Aid. Details regarding the subject Memory Aid are included in the MOP for this study.

6.4.2 Day 2 – Inpatient CRU

- Obtain vital signs 24 hours (±30 min) after resting in a supine or semi-supine position for at least 5 minutes.
- Perform targeted PE.

- Obtain blood for hematology/coagulation/chemistry and urine for urinalysis.
- Obtain PK blood sample 24 hours (±30 min) after dosing. No PK blood samples collected in Cohort 1.
- Assess reactogenicity at SC injection site at 24 h (±30 min) post-dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.

6.4.3 Day 3 – Inpatient CRU

- Obtain PK blood sample 48 hours (±30 min) after dosing. No PK blood samples collected in Cohort 1.
- Assess reactogenicity at SC injection site(s) at 48 h (±30 min) post-dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.

6.4.4 Day 4 – Inpatient CRU

- Obtain resting vital signs 72 h (±30 min) after being at rest for at least 5 minutes.
- Perform targeted PE.
- Assess reactogenicity at SC injection site(s) at 72 h (±30 min) post-dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.

6.4.5 Day 5 – Inpatient CRU

- Obtain PK blood sample 96 hours (±30 min) after dosing. No PK blood samples collected in Cohort 1.

- Assess reactogenicity at SC injection site(s) at 96 h (±30 min) post-dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.

6.4.6 Day 6 – Inpatient CRU

- Assess reactogenicity at SC injection site(s) at 120 h (±30 min) post-dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.

6.4.7 Day 7 – Inpatient CRU

- Obtain resting vital signs 144 hours (±30 min) after being at rest for at least 5 minutes.
- 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).
- Perform targeted PE.
- Obtain blood for hematology/coagulation/chemistries and urine for urinalysis.
- Obtain PK blood sample 144 hours (±30 min) after dosing. No PK blood samples collected in Cohort 1.
- Assess reactogenicity at SC injection site(s) at 144 h (±30 min) post-dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.

- Counsel on contraceptive use and provide post-discharge instructions (dietary and medication/nonmedication, vaccine and blood/blood product/sperm donation restrictions).
- Train on proper completion of Memory Aid.
- Subject discharge from CRU after all procedures are completed.

6.4.8 Day 14 (±1 Day) – Follow-Up - Outpatient

- Obtain resting vital signs after being at rest for at least 5 minutes.
- Obtain PK blood sample. No PK blood samples collected in Cohort 1.
- Assess reactogenicity at SC injection site(s) (see Section 7.1.4 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.
- Review Memory Aid.
- Reminder of contraceptive use and post-discharge instructions (dietary and medication/nonmedication, vaccine and blood/blood product/sperm donation restrictions).

6.4.9 Day 21 (±1 Day) – Telephone Follow-Up

- Interview subjects for changes at SC injection site(s); refer subjects for unscheduled visit if changes at SC injection site(s) reported.
- Review Memory Aid.
- Remind subjects to report changes at SC injection site(s) immediately.

6.4.10 Day 30 (±1 Day) – Follow-Up – Final Study Visit

- Obtain resting vital signs after being at rest for at least 5 minutes.
- 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).
- Perform targeted PE.
- Obtain weight, calculate BMI.
- Obtain blood for hematology/coagulation/chemistry and urine for urinalysis.
- Perform serum pregnancy test (females of childbearing potential only).
- Obtain PK blood sample. No PK blood samples collected in Cohort 1.
- Assess reactogenicity at SC injection site(s) (see Section 7.1.3 and MOP for this study).
- Assess AEs.
- Review Memory Aid.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.
- Review post-study instructions (contraceptive use, pregnancy reporting).

6.5 Part 2 (Cohorts 7 through 10)

6.5.1 Days 1, 8, and 15 – Inpatient CRU

Study drug or placebo will be administered via SC injection in the morning on Days 1, 8, and 15. Subjects will be inpatients in the CRU and will undergo the following procedures, which are listed in the Schedule of Study Procedures and Evaluations (Appendix A) and detailed in Clinical Evaluations (Section 7):

- Randomize the subject (Day 1 only).
- Review inclusion criteria numbers 2-7 and 10-11, and exclusion criteria numbers 2-4 and 8-18 (from Section 5.1.2) to ensure the subject remains eligible for dosing (Days 8 and 15 only).
- Obtain resting vital signs before study drug dosing (within 60 minutes of study drug dosing for Day 1). This is to be documented as the Baseline prior to dosing on Day 1.
- Perform targeted PE.
- Obtain a 12-lead ECG before study drug dosing (Day 1 only) after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period) and within 60 minutes before study drug dosing.
- Baseline (Day 1) and pre-dose (Days 8 and 15) skin assessment at SC injection site area(s) prior to study drug dosing (see Section 7.1.3 and MOP for this study).
- Administer study drug via SC injection in the abdomen at a slow, steady pace.
- Obtain vital signs at 15 minutes (±5 min), 1 hour (±10 min), and 2 hours (±10 min) after dosing, after resting in a supine or semi-supine position for at least 5 minutes.
- 12-lead ECG at 4 hours (±10 minutes) after injection after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).
- Obtain PK blood samples within 60 minutes prior to study drug dosing (for Day 1) and at 0.5 h (±5 min), 1 h (±10 min), 2 h (±10 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), and 12 h (±10 min) after dosing (Days 1 and 15); or within 15 minutes prior to dosing and at 1 h (±10 min), and 4 h (±10 min) after dosing (Day 8 only).
- Assess reactogenicity at SC injection site(s) at 1 h (±10 min) and 4 h (±10 min) post-dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since administration to the CRU,
- Issue Memory Aid. Details regarding the subject Memory Aid are included in the MOP for this study.

6.5.2 Days 2, 9, and 16 – Inpatient CRU

- Obtain resting vital signs 24 hours (±30 min) after being at rest for at least 5 minutes.
- Perform targeted PE.
- Assess reactogenicity at SC injection site(s) at 24 h (±30 min) post dose (see Section 7.1.3 and MOP for this study).
- Obtain blood for hematology/coagulation/chemistry and urine for urinalysis.
- Obtain PK blood sample 24 hours (±30 min) after dosing (Days 2 and 16 only).
- Assess AEs.

6.5.3 Days 3, 10, and 17 – Inpatient CRU

- Obtain PK blood sample 48 hours (±30 min) after dosing (Days 3 and 17 only).
- Assess reactogenicity at SC injection site(s) at 48 h (±30 min) post dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.

6.5.4 Days 4, 11, and 18 – Inpatient CRU

- Obtain resting vital signs 72 hours (±30 min) after being at rest for at least 5 minutes.
- Perform targeted PE.

- Assess reactogenicity at SC injection site(s) at 72 h (±30 min) post dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.

6.5.5 Days 5, 12, and 19 – Inpatient CRU

- Obtain PK blood sample 96 hours (±30 min) after dosing.
- Assess reactogenicity at SC injection site(s) at 96 h (±30 min) post dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.

6.5.6 Days 6, 13, and 20 – Inpatient CRU

- Assess reactogenicity at SC injection site(s) at 120 h (±30 min) post dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.

6.5.7 Days 7, 14, and 21 – Inpatient CRU

- Obtain resting vital signs 144 hours (±30 min) after being at rest for at least 5 minutes.
- 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period). (Day 21 only)
- Perform targeted PE.
- Obtain blood for hematology/coagulation/chemistry and urine for urinalysis.
- Obtain PK blood sample 144 hours (±30 min) after dosing.
- Assess reactogenicity at SC injection site(s) at 144 h (±30 min) post dose (see Section 7.1.3 and MOP for this study).

- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.
- Counsel on contraceptive use and provide post-discharge instructions (dietary and medication/nonmedication, vaccine and blood/blood product/sperm donation restrictions).
- Train on proper completion of Memory Aid (Day 21 only).
- Subject discharge from CRU after all procedures completed (Day 21 only).

6.5.8 Day 30 (±1 Day) – Follow-Up - Outpatient

- Obtain resting vital signs after being at rest for at least 5 minutes.
- 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).
- Perform targeted PE.
- Obtain PK blood sample.
- Assess reactogenicity at SC injection site(s) (see Section 7.1.3 and MOP for this study).
- Assess AEs.
- Review Memory Aid.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since discharge from the CRU.
- Reminder of contraceptive use and post-discharge instructions (dietary and medication/nonmedication, vaccine and blood/blood product/sperm donation restrictions).

6.5.9 Day 45 (±1 Day) – Follow-Up – Final Study Visit

- Obtain resting vital signs after being at rest for at least 5 minutes.
- 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).
- Perform targeted PE.
- Obtain weight, calculate BMI.
- Obtain blood for hematology/coagulation/chemistry and urine for urinalysis.
- Perform serum pregnancy test (females only).
- Obtain PK blood sample.
- Assess reactogenicity at SC injection site(s) (see Section 7.1.4 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since Day 30.
- Review Memory Aid.
- Review post-study instructions (contraceptive use, pregnancy reporting).

6.6 Part 3 (Cohort 11)

6.6.1 Days 1 and 22 – Inpatient CRU

For Cohort 11, the subject will be randomized to sequence and either the study drug will be administered via SC injection in the morning on Day 1 and as an IV infusion over 60 (±5) minutes in the morning on Day 22; or the study drug will be administered via IV infusion over 60 (±5) minutes in the morning on Day 1 and via SC injection in the morning on Day 22. Subjects will be inpatients in the CRU and will undergo the following procedures, which are

listed in the Schedule of Study Procedures and Evaluations (Appendix A) and detailed in Clinical Evaluations (Section 7):

- Randomize the subject (Day 1 only).
- Review inclusion criteria numbers 2-7 and 10-11, and exclusion criteria numbers 2-4 and 8-18 (from Section 5.1.2) to ensure the subject remains eligible for dosing (Day 22 only).
- Obtain resting vital signs before study drug dosing (within 60 minutes of study drug dosing. This is to be documented as the Baseline prior to dosing on Day 1.
- Perform targeted PE.
- Obtain a 12-lead ECG within 60 minutes of study drug dosing, (Day 1 only), after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).
- Baseline skin assessment at SC injection site area prior to study drug dosing: assess reactogenicity at SC injection site before study drug dosing on Day 22 (see Section 7.1.3 and MOP for this study).
- Administer study drug.
- Obtain vital signs (SC): at 15 minutes (±5 min), 1 hour (±10 min), and 2 hours (±10 min) after dosing, after resting in a supine or semi-supine position for at least 5 minutes.
- Obtain vital signs (IV): at 15 minutes (±5 min), 1 hour (±10 min), and 2 hours (±10 min) after start of infusion, and after resting in a supine or semi-supine position for at least 5 minutes.
- Obtain PK blood samples within 60minutes before study drug dosing and at 0.5 h (±5 min), 1 h (±10 min), 2 h (±10 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), and 12 h (±10 min) after the start of infusion or injection.
- Post dose ECG (SC) at 4 hours (±10 minutes) after SC injection, 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).

- Post dose ECG (IV) at 1 hour (±10 minutes) from beginning of IV infusion, 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).
- Assess reactogenicity at SC injection site at 1 h (±10 min) and 4 h (±10 min) post dose (see Section 7.1.3 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.
- Issue Memory Aid (Day 1 only). Details regarding the subject Memory Aid are included in the MOP for this study.

6.6.2 Days 2 and 23 – Inpatient CRU

- Obtain resting vital signs 24 hours (±30 min) after being at rest for at least 5 minutes.
- Perform targeted PE.
- Assess reactogenicity at SC injection site at 24 h (±30 min) post dose (see Section 7.1.4 and MOP for this study).
- Obtain blood for hematology/coagulation/chemistry and urine for urinalysis.
- Obtain PK blood sample 24 hours (±30 min) after dosing.
- Assess AEs.

6.6.3 Days 3 and 24 – Inpatient CRU

- Obtain PK blood sample 48 hours (±30 min) after dosing.
- Assess reactogenicity at SC injection site at 48 h (±30 min) post dose (see Section 7.1.4 and MOP for this study).
- Assess AEs.

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.

6.6.4 Days 4 and 25 – Inpatient CRU

- Obtain resting vital signs 72 hours (±30 min) after being at rest for at least 5 minutes.
- Perform targeted PE.
- Assess reactogenicity at SC injection site at 72 h (±30 min) post dose (see Section 7.1.4 and MOP for this study).
- Assess AEs.

6.6.5 Days 5 and 26 – Inpatient CRU

- Obtain PK blood sample 96 hours (±30 min) after dosing.
- Assess reactogenicity at SC injection site at 96 h (±30 min) post dose (see Section 7.1.4 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.

6.6.6 Days 6 and 27 – Inpatient CRU

- Assess reactogenicity at SC injection site at 120 h (±30 min) post dose (see Section 7.1.4 and MOP for this study).
- Assess AEs.

6.6.7 Days 7 and 28 – Inpatient CRU

- Obtain resting vital signs 144 hours (±30 min) after being at rest for at least 5 minutes.
- Perform targeted PE.

- Obtain blood for hematology/coagulation/chemistry and urine for urinalysis.
- Obtain PK blood sample 144 hours (±30 min) after dosing.
- Assess reactogenicity at SC injection site at 144 h (±30 min) post dose (see Section 7.1.4 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU.
- Counsel on contraceptive use and provide post-discharge instructions (dietary and medication/nonmedication, vaccine and blood/blood product/sperm donation restrictions),
- Train on proper completion of Memory Aid (Day 7), refresher (Day 28).
- Subject discharge from CRU after all procedures completed.

6.6.8 Days 14 (±1 Day) and 35 (±1 Day) – Follow-Up - Outpatient

- Obtain vital signs after resting in a supine or semi-supine position for at least 5 minutes.
- Perform targeted PE.
- Obtain PK blood sample.
- Assess reactogenicity at SC injection site (see Section 7.1.4 and MOP for this study).
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since discharge from the CRU.
- Review Memory Aid.
- Reminder of contraceptive use and post-discharge instructions (dietary and medication/nonmedication, vaccine and blood/blood product/sperm donation restrictions).

6.6.9 Day 52 (±1 Day) – Follow-Up – Final Study Visit

- Obtain vital signs after resting in a supine or semi-supine position for at least 5 minutes.
- 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period).
- Perform targeted PE.
- Obtain weight, calculate BMI.
- Obtain blood for hematology/coagulation/chemistry and urine for urinalysis.
- Perform serum pregnancy test (females only).
- Obtain PK blood sample.
- Assess AEs.
- Review and record any concomitant medications and non-pharmacologic treatments/procedures since Day 35.
- Review Memory Aid.
- Review post-study instructions (contraceptive use, pregnancy reporting).

6.6.10 Early Termination (ET) Visit (if needed)

The CRU will make every effort to perform all assessments listed for the last scheduled FU visit if a subject is terminated prematurely from this trial. All information collected will be documented in eCRFs or study records.

6.7 Unscheduled Study Visits

Subjects will return to the CRU at the direction of the Site PI for FU and data from unscheduled visits or procedures (if any) and will be captured and presented in data listings. These data will be clearly identified as unscheduled observations. Safety assessments, including updated history, AEs, PE, and any other trial procedures deemed necessary by the PI, will be obtained.

Subjects returning to the CRU for unscheduled visit(s) may undergo procedures, including but not limited to, the following, which are listed in the Schedule of Study Procedures and Evaluations (Appendix A) and detailed in Clinical Evaluations (Section 7):

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since last visit,
- Obtain a 12-lead ECG after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period),
- Obtain blood for hematology/coagulation/chemistry and urine for urinalysis,
- Perform targeted PE including resting vital signs (heart rate, blood pressure, oral temperature, and respiration rate, taken after resting for at least 5 minutes). If abnormal, these measurements may be repeated once,
- Review Memory Aid,
- Assess AEs.

6.8 Protocol Deviations

A protocol deviation is any noncompliance with this protocol, 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 will be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
5.1 Quality Assurance (QA) and Quality Control (QC), Section 5.1.1
5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the Site PI and personnel to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the Statistical and Data Coordinating Center (SDCC) protocol deviation reporting procedures.

All protocol deviations, as defined above, must be addressed in subject data collection forms (DCFs). Protocol deviations must be sent to the local IRB/IEC per their guidelines. The Site PI and personnel are responsible for knowing and adhering to their IRB requirements.

7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

7.1 Clinical Evaluations

7.1.1 Medical History

Medical history will be obtained by direct interview. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic, nervous system, blood, lymph glands, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited. The medical history will include current and past medical diagnoses, hospitalizations and major surgical procedures. Demographic information (date of birth, gender, race, ethnicity) will be obtained as part of the medical history assessment. The medical history will be obtained at screening and updated upon admission to the CRU on Day -1.

7.1.2 Height, Weight, Body Mass Index (BMI)

All subjects will have height measured (at Screening only) and be weighed following the CRU's standard operating procedures at Screening, Day -1 and at the final study visit. BMI is calculated as: (weight in kg divided by height in m, squared). Subjects who no longer meet inclusion criteria due to changes in weight or BMI after dosing remain eligible and will not be removed from the study.

7.1.3 Physical Examinations

A complete PE at Screening will evaluate vital signs (taken after resting for at least 5 minutes); general appearance; head, eyes, ears, nose, and throat; neck; chest and lungs; cardiovascular system, abdomen, musculoskeletal system, lymph nodes, extremities/skin, and neurological system.

A targeted PE will evaluate resting vital signs, skin, and suspected organ systems described in any solicited or unsolicited AEs, at times specified in Appendix A.

7.1.4 Local Reactogenicity Symptoms

Reactogenicity assessments will include an assessment of AEs occurring after dose administration on Day 1 through Day 30 of Part 1 (SAD), Day 30 of Part 2 (MAD) or Day 35 of

Part 3 (BA), which includes an assessment of SC injection site reactions (see Additional Characterization of Reactogenicity at Injection Sites, below). Pre-administration (baseline) injection site skin assessments will be performed prior to each study injection to establish baseline, then the study injection will be given.

The study SC injection site(s) will be examined pre-dose and at 1 and 4 h (±10 minutes), 24, 48, 72, 96, 120, 144 h (±30 minutes) post-administration in all cohorts (SAD/MAD/BA). Additional injection site examinations will occur on Day 14 of Part 1 (SAD), Day 30 of Part 2 (MAD), and Days 14 and 35 of Part 3 (BA), and any AE/SAEs will be recorded on the appropriate data collection form.

Additional Characterization of Reactogenicity at Injection Sites

Lesions at the injection site will be characterized by the study site staff as follows:

1. Ecchymosis: non-raised skin discoloration caused by the escape of blood into the tissues from ruptured blood vessels

2. Erythema: localized redness

3. Induration: (hardness)/swelling

4. Nodule: solid or cystic raised bump in the skin

5. Ulcer: an open lesion on the surface of the skin caused by superficial loss of tissue. NOTE: Ulcers at the injection site, regardless of size or severity, are of special interest and must be measured as well as photographed*, according to the MOP for this study. Please see Section 8.1.3 for reporting details and Section 8.7 for halting rules.

6. Healed**: previously observed lesion that has dried up without any persistent induration or ulcer.

7. Scar**: replacement of normal skin with fibrous tissue

*All SC site reactions will be photographed at each visit, scheduled and unscheduled until resolution.

**Recorded, but not graded.

7.1.5 Vital Signs

Vital signs (body temperature, heart rate, respiration rate, and blood pressure) will be obtained at times specified in Appendix A. Vital signs will be measured after resting at least 5 minutes. The pre-dose vital signs on days of dosing will be measured within 60 minutes of study drug dosing; Day 1 post-dose vital signs measurements should be taken within ± 5 minutes of the 15-minute post-dose timepoint and within ± 10 minutes for additional post-dose timepoints. Other vital signs during the inpatient stay will be taken within ±30 minutes of the nominal timepoint. For outpatient visits, vital signs will be measured within the visit window.

Day 1 post-dose timepoints for vital sign measurements for the IV portion of Part 3 will be based on the start of infusion.

7.1.6 Electrocardiograms

Standard 12-lead ECGs to assess heart rate, rhythm, and PR, QRS, QT, and QTc interval durations will be obtained at times specified in Appendix A.

ECGs (triplicate readings, at least 1 minute apart within a 15-minute period), will be taken after at least 5 minutes in the supine position. The pre-dose ECGs on days of dosing will be taken within 60 minutes of study drug dosing. Post dose ECGs on days of dosing will be taken at 4 hours (±10 minutes) after SC dosing. Post dose ECGs on days of dosing will be taken at 1 hour (±10 minutes) from start of infusion for IV administration in Part 3.

ECGs will also be taken at the following timepoints:

- Day 7, Day 30, and Unscheduled visits for SAD
- Day 21, Day 30, Day 45, and Unscheduled visits for MAD
- Day 52 and Unscheduled visits for BA

The screening ECG will be used by the PI to determine a subject's eligibility for enrolment. The Day 1 pre-dose ECG will be reviewed to determine if subjects can be dosed.

All ECGs will be reviewed by the PI or designee. ECGs with the following readings will be considered acceptable for trial participation and will not be considered abnormal for trial purposes unless the PI or physician designee believes they represent a new medical condition when compared to baseline ECGs. In such cases an AE will be documented, and the subject will be followed for safety evaluations as appropriate. The following pre-existing conditions identified at enrolment will not be considered AEs:

- Sinus bradycardia,
- Sinus arrhythmia,
- Subjects without a history of prolonged QTc and an abnormal QTc interval at Screening will undergo repeat ECG assessment within the screening period before randomization to confirm prolongation. If the repeat ECG QTcF is within normal limits (see Appendix B) the subject may be considered for enrolment.

The Sponsor may review all or individual screening ECGs or may delegate to determine if meets intention of entry criteria goal of enrolling healthy normal subjects.

If a subject has possible cardiac-related symptoms, repeat ECGs will be obtained every 30 minutes (±3 minutes) until the waveform reverts to its baseline appearance, or symptoms resolve, or are determined not to be cardiac-related. Subjects with cardiac-related symptoms that are associated with ECG changes will be transferred to appropriate emergency department for further evaluation and treatment at the discretion of the PI.

7.1.7 Assessment of Concomitant Medications/Treatments Other than Study Product

Subjects are required to abide by the following rules regarding intake of medications and other substances before and during the study:

1) Refrain from the use of any prescription medications (with the exception of hormonal contraceptives), within 14 days before the first study drug administration and until after the final study visit.
2) Refrain from the use of over-the-counter medications including vitamins, supplements, and herbal supplements (except for acetaminophen or ibuprofen) within 14 days before the first study drug administration,
3) The use of tobacco product, including smoking and the use of snuff and chewing tobacco, and other nicotine or nicotine-containing products (including patches), is not permitted by a subject within 90 days of Screening for the study or while a subject is enrolled in the study. A urine test for cotinine will be performed at Screening and upon admission to the CRU.
4) Refrain from consuming foods or beverages containing the following substances for the duration of the study:
5) Alcohol: ≤48 hours before the first study drug administration until discharge. A urine alcohol test will be performed at Screening and upon admission to the CRU.

6) Xanthines/caffeine: ≤24 hours before the first study drug administration and until discharge.
7) Refrain from receiving a live or killed vaccine, or immunoglobin, within 14 days prior to dosing.
8) The use of illegal drugs is not permitted while a subject is enrolled in this study. A urine drug test will be performed at Screening and upon admission to the CRU.
9) Previous participation in this trial, any other rezafungin trial, or any trial involving administration of drug product within 28 days of study drug dosing. Plans to enroll in another clinical trial that could interfere with safety assessment of the investigational product at any time during the study period;

If a subject is unable to comply with the restrictions described above, the subject's continued participation in the study will be re-evaluated by the Investigator, in consultation with the Medical Monitor.

7.2 Laboratory Evaluations

7.2.1 Clinical Laboratory Evaluations

All laboratory assessments will be done by the clinical site's certified laboratory. Laboratory toxicity grading will be determined by use of the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007 and the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007, as modified for this study and appropriate for the administration of rezafungin (Appendix B. Toxicity Grading Criteria for Normal Human Subjects).

At Screening, laboratory test values that fall outside the reference range on the laboratory reports and deemed not clinically significant by the Investigator may be repeated at the discretion of the Investigator (to assess for transitional conditions). Laboratory values that fall outside of the reference range on Day -1 (baseline), may not be repeated, and subject will be withdrawn from the study. (See Note below for exceptions).

If a single repeat Screening evaluation is within the reference range, the subject may be further considered for study eligibility.

Note: Hematuria during active menses causing urinalysis results outside the reference range will not be considered clinically significant (not an AE).

Viral Serology Testing

Subjects will be screened for HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody. These tests must be negative for eligibility into this trial. In cases where a false positive result is suspected, confirmatory testing may be performed (e.g., Polymerase Chain Reaction).

Drug, Alcohol, and Cotinine Testing

The urine toxicology screen will be performed to detect the presence of amphetamines, barbiturates, cocaine, opiates, cannabinoids, phencyclidine, and benzodiazepines. The results must be negative for eligibility into this trial. A urine alcohol test will also be performed to detect alcohol use and must be negative prior to randomization. A urine cotinine test will also be performed to detect nicotine use and must be negative prior to randomization.

Follicle Stimulating Hormone (FSH) and Pregnancy Testing

For women of child-bearing potential, a serum pregnancy test will be done at screening and must be negative for eligibility into this trial. A serum pregnancy test will be done on Day -1, which must be reported as negative before dosing. A serum pregnancy test will be repeated at the final trial visit. Perform FSH test in postmenopausal females only, prior to randomization.

Safety Laboratory Tests

The following laboratory tests will be performed as specified in Appendix A. Subjects will be fasting. This means no food or drink (other than water) for at least 8 hours before sampling.

- Hematology: complete blood count (CBC) with differential (red blood cell count, total and differential white blood cell counts, hemoglobin, hematocrit, and platelet count),
- Coagulation; (activated partial thromboplastin time [APTT], prothrombin time [PT}, and international normalized ratio [INR]),

- All subjects must undergo clinical chemistry testing (albumin, glucose, blood urea nitrogen or urea, potassium, calcium, sodium, chloride, total protein, creatinine, total carbon dioxide (CO2), creatine phosphokinase (CK), phosphorus, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin at Screening and Baseline to assess protocol eligibility. Clinical chemistry tests will be performed thereafter as specified in the Schedule of Assessments and Procedures Appendix A. Subjects must fast a minimum of 8 hours before blood collection for a clinical chemistry panel.

- Dipstick urinalysis: protein, blood, and glucose must be negative or trace (complete urinalysis to be performed if dipstick urinalysis is positive for blood). Menstruating females failing inclusion criteria due to a positive result may be retested following cessation of menses. Do not exclude subjects with >5 red blood cells/high power field if menstruating.

Laboratory values will be entered in the Clinical Labs eCRF.

7.2.2 Research Assays

Bioanalytical Assay

Plasma concentrations of rezafungin in EDTA will be determined by a validated LC-MS/MS method. Details are provided in the MOP for sample collection time in each cohort for SAD (except cohort 1), MAD, and BA.

For Part 1/SAD blood samples will be collected at the following scheduled timepoints for Cohorts 2, 3, 4, 5, and 6 (see Table 5). For Part 2/MAD, blood samples will be collected at the following scheduled timepoints for Cohorts 7, 8, 9, and 10 (see Table 6). For Part 3/BA, blood samples will be collected at the following scheduled timepoints for Cohort 11 (see Table 7).

Table 5: Blood Sampling Timepoints for Rezafungin Pharmacokinetic Analysis Cohorts 2, 3, 4, 5 and 6 SAD (Part 1)

Dosing Day	Timepoint						
Day 1 (pre-dose)	Taken within 60 minutes before study drug dosing						
Day 1 (hours post-dose)	0.5	1	2	4	6	8	12
Day 2 (hours post-dose)	24						
Day 3 (hours post-dose)	48						
Day 5 (hours post-dose)	96						
Day 7 (hours post-dose)	144						
Day 14	±1 Day						
Day 30	±1 Day						

Table 6: Blood Sampling Timepoints for Rezafungin Pharmacokinetic Analysis Cohorts 7, 8, 9, and 10 MAD (Part 2)

Dosing Day	Timepoint						
Day 1, 8, and 15 (pre-dose)	For Day 1 taken within 60 minutes before study drug dosing and for Days 8 and 15, taken within 15 minutes before study drug dosing						
Day 1 and 15 (hours post-dose)	0.5	1	2	4	6	8	12
Day 2 and 16 (hours post-dose)	24						
Day 3 and 17 (hours post-dose)	48						
Day 5, 12, and 19 (hours post-dose)	96						
Day 7, 14, and 21 (hours post-dose)	144						
Day 8 (hours post dose)	1 and 4	1		4			
Day 30	±1 Day						
Day 45	±1 Day						

Table 7: Blood Sampling Timepoints for Rezafungin Pharmacokinetic Analysis Cohort 11 BA (Part 3)

Dosing Day	Timepoint						
Day 1 and 22 (pre-dose)	Taken within 60 minutes before study drug dosing						
Day 1 and 22 (hours post-dose*)	0.5	1	2	4	6	8	12
Day 2 and 23 (hours post-dose*)	24						
Day 3 and 24 (hours post-dose*)	48						
Day 5 and 26 (hours post-dose*)	96						
Day 7 and 2 (hours post-dose*)	144						
Day 14 and 35	±1 Day						
Day 52	±1 Day						

*Post-dose timepoints for PK blood sampling for the IV portion of Part 3 will be based on the start of infusion

Laboratory Specimen Preparation, Handling, and Storage

Detailed instructions for plasma and urine for drug testing and urinalyses specimen preparation, handling and storage are outlined in the MOP for this study.

Total Blood Volume Drawn

The total volume of blood that will be drawn from each subject is described in Table 8:

Table 8: Total Volume of Blood Drawn From Each Subject - Part 1 (SAD) Cohorts 1-6

Laboratory Test	**Sample Volume (mL)**	**Number of Samples**	**Total Volume (mL)**
Safety:			
Clinical chemistry	4	5	20
Hematology	2	5	10
Coagulation	2.7	5	13.5
Serology	4	1	4
Pharmacokinetic:*	3	14	42
When using an indwelling catheter 1.0 mL of blood will be removed prior to sample collection			
Total	15.7	30	89.5
Cohort 1 Total*	12.7	16	47.5

*No PK blood samples collected in Cohort 1.

Table 9: Total Volume of Blood Drawn From Each Subject - Part 2 (MAD) Cohorts 7-10

Laboratory Test	**Sample Volume (mL)**	**Number of Samples**	**Total Volume (mL)**
Safety:			
Clinical chemistry	4	9	36
Hematology	2	9	18
Coagulation	2.7	9	24.3
Serology	4	1	4
Pharmacokinetic:	3	27	81
When using an indwelling catheter 1.0 mL of blood will be removed prior to sample collection			
Total	15.7	55	163.3

Table 10: Total Volume of Blood Drawn From Each Subject - Part 3 (BA) Cohort 11

Laboratory Test	**Sample Volume (mL)**	**Number of Samples**	**Total Volume (mL)**
Safety:			
Clinical chemistry	4	7	28
Hematology	2	7	14
Coagulation	2.7	7	18.9
Serology	4	1	4
Pharmacokinetic:	3	27	81
When using an indwelling catheter 1.0 mL of blood will be removed prior to sample collection			
Total	15.7	43	145.9

Laboratory PK Specimen Shipping

All PK specimens will be shipped to the Fisher Biorepository for storage and/or transfer to the ICON ABL. Detailed instructions for shipping plasma are outlined in the MOP for this study.

8 ASSESSMENT OF SAFETY

8.1 Assessing and Recording Safety Parameters

Regulatory requirements including FDA regulations, ICH Guidelines for GCP, and European Union Clinical Trials Directive set forth safety monitoring and reporting responsibilities of the Sponsors and Site PI to ensure the safety and protection of human subjects participating in clinical trials.

Responsibilities

Site PIs participating in this trial are responsible for and will:

- Evaluate subject safety including assessment of AEs for seriousness, severity, and causality;
- notify the Sponsor of SAEs immediately;
- provide detailed written reports, including necessary documentation requested by the Sponsor or IRB/IEC, promptly following immediate initial reports;
- inform the IRB/IEC of AEs as requested by applicable regulatory requirements.

8.1.1 Adverse Events

ICH 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. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of 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, including solicited local (injection site), starting from administration of the first dose of study drug until the final study visit will be captured on the appropriate data DCF 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 Form FDA 1572 as a PI), date of resolution, seriousness and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution or until assessed to be stable by the PI.

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.

Adverse Events Grading

All AEs (laboratory and clinical symptoms) will be graded for severity and assessed for relationship to study product (see definitions). Abnormalities present at baseline will not be reported as AEs unless worsening in severity post-dosing. AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate DCF and eCRF. For vital sign AEs, when multiple readings are taken within the same day the AE of highest severity will be documented to allow an assessment of the duration of the AE from the highest level of intensity. If a subject was enrolled in the trial with a laboratory value that is outside the reference range, but within the acceptable ranges, an AE will be recorded if it otherwise meets the definition of AE in Section 8.1.1 and the on-study value is higher (if initially high) or lower (if initially low) than the screening value.

Severity of Event:

AEs will be assessed by the Site PI using a protocol-defined grading system (Appendix B). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify 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 subject,

Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

Relationship to Study Product: The assessment of the AE's relationship to study product will be done by the licensed study physician indicated on 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 trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical trial, the study product must always be suspect. The relationship to study product will be assessed for AEs using the terms related or not related:

Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE,

Not Related – There is not a reasonable possibility that the administration of the study product caused the AE.

8.1.2 Serious Adverse Events

An AE or suspected adverse reaction is considered a SAE if, in the view of either the Site PI or Sponsor, it results in any of the following outcomes:

Death,

a life-threatening adverse AE[1],

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, skin ulcers (open sores) at the injection site, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

[1] 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 Form FDA 1572 or by the Site PI or Sub-Investigator.

Recorded on the appropriate SAE DCF and eCRF.

Followed through resolution by a licensed study physician (for Investigation New Drug (IND) studies, a physician listed on Form FDA 1572 as the Site PI or Sub-Investigator).

Reviewed and evaluated by DMID, an Independent Safety Monitor (ISM) (as deemed necessary), the SMC (periodic review unless related), and the IRB/IEC.

8.1.3 Adverse Events of Special Interest

In addition to SAEs, the following adverse events of special interest (AESIs) should be promptly reported to the Sponsor even if the nature of the adverse event is deemed non-serious according to the usual regulatory criteria.

Intravenous Infusion Intolerability

Events that, in the opinion of the Investigator, may represent intolerance of the IV infusion of the study drug must be recorded as AEs on the eCRF. In general, these events would be temporally associated with the IV infusion of the Sponsor's study drug.

Phototoxicity

Due to preliminary results from a nonclinical phototoxicity study in rats, subjects should be advised to avoid sun exposure without adequate protection. Site PIs should report any AE potentially related to phototoxicity to the Sponsor.

Neuropathy and Tremors

In a rezafungin 3-month toxicity study in monkeys, there were observations of tremors, and histology consistent with axonal degeneration (potentially consistent with clinical presentation of neuropathy) first appearing at Week 6 of dosing and at 11-fold the exposure for the rezafungin for Injection dose in this study. Ataxia, axonal neuropathy, hypoesthesia, paresthesia, peripheral

motor neuropathy, peripheral neuropathy, peripheral sensory neuropathies, peripheral sensorimotor neuropathy, polyneuropathy, toxic neuropathy, and tremors should be considered AESIs. Site PIs should report any AE potentially related to neuropathy to the Sponsor.

Skin Ulcers

Skin ulcerations of any grade at study drug injection sites will be of special interest. Site PIs should report any skin ulcerations at injection sites to the Sponsor within 24 hours of site awareness. Sponsor will report skin ulcerations at injection sites to the FDA as per Expedited Reporting guidelines. Any skin ulcerations at site(s) of injection will be assessed daily while inpatient; following discharge from the unit, the Site PI will determine the frequency of monitoring until resolution or stabilization. The status of skin ulcerations will be followed until resolution.

8.2 Specification of Safety Parameters

Safety will be assessed by the frequency and severity of AEs following administration of rezafungin.

8.2.1 Injection Site Reactogenicity

The local injection site(s) will be assessed for reactogenicity with respect to symptoms. All Skin reactions at the injection site will also be measured and photographed, according to the MOP for this study. See Appendix B and Section 7.1.4 for additional information.

8.2.2 New-Onset Chronic Medical Conditions

New-Onset Chronic Medical Conditions are defined as any new International Class of Diseases, Tenth Revision diagnosis that is applied to the subject during this trial, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.

8.2.3 Dose Escalation Criteria

Dose escalation to each successive cohort of subjects will occur if none of the predefined dose escalation halting criterion is met (for all subjects through Day 30 [SAD] or Day 30 [MAD]). The SDCC will provide notification to the PI upon analysis of data for the cohort (for all subjects through Day 30 [SAD] or Day 30 [MAD]) for halting criteria as described in Section 8.7 Study

Design, Objectives and Endpoints or Outcome Measures, Dose Escalation. If any of the criterion for dose escalation is met, or, at the discretion of the PI or DMID Medical Monitor, the study enrollment and dosing will be stopped until the SMC reviews the data and provides its recommendations. There will be a scheduled SMC data review meeting prior to start of Part 2 (MAD).

8.3 Reporting Procedures

8.3.1 Reporting Serious Adverse Events

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an 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 Advantage EDC. 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.

8.4 Type and Duration of Follow-Up of Subjects after Adverts Events

The site will send a copy of the SAE report(s) to the ISM (as deemed necessary) 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 principal investigator 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.

8.4.1 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the Site PI, DMID, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the AE. DMID will notify FDA and all participating PI's (i.e., all PI's to whom the Sponsor is providing drug under its IND or under the PI's IND[s]) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of 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. Relevant FU information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to 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 serious events designated as "not related" to study drug will be reported to the FDA at least annually in a summary format.

8.4.2 Reporting of Pregnancy

A Notification of Pregnancy form will be completed for any female study subject or for any female partner of a male study subject who becomes pregnant following their exposure to study product (Day 1) through 4 months (120 days) after the last dose of study product is administered. The site will discuss pregnancy reporting with subjects at the Final Study visit with instructions and provide contact information in case pregnancy occurs. The pregnant subject will be followed by monthly telephone calls until 2 months after the birth of the baby or until the end of the pregnancy (in case pregnancy is terminated) at which time the Pregnancy Outcome form will be completed. Infants born to these study subjects will also be monitored for SAEs for up to 2 months after birth (information regarding SAEs will be captured on the Pregnancy Outcome form and the SAE form). If an SAE occurs during the pregnancy, the SAE will be reported on the appropriate SAE form and provided to DMID pharmacovigilance. Pregnancy Outcome forms will be used to collect, but not be limited to, data on the following information, should it be

identified during the monthly telephone calls, at the end of the pregnancy, or at the follow-up telephone call at 2 months after birth of the baby:

1. Prior maternal history including congenital abnormalities or pregnancy complications;
2. Estimated date of conception;
3. Estimated and actual date of delivery or pregnancy termination;
4. Mode of delivery;
5. Maternal complications;
6. Neonatal complications (i.e. lethal or nonlethal congenital abnormality).

8.5 Type and Duration of Follow-Up of Subjects after Adverse Events

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

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

Laboratory values will be graded according to Appendix B. Abnormal laboratory values, performed as part of hematology, chemistry panel, or urinalysis but not listed in Appendix B, will be evaluated by the study clinicians, recorded in the source document and, if clinically significant, considered AEs and graded according to the criteria details described in Section 8.1.

The site principal investigator or appropriate sub-investigator is responsible for recording all AE and SAEs that are observed or reported during this study, regardless of the relationship to study product. AE and SAEs or abnormal clinical findings will be collected, assessed, documented, reported, and followed appropriately.

8.7 Halting Rules

8.7.1 Study Halting Rules

Trial dosing can be halted at any time if medically indicated. Trial dosing will be stopped, and all available safety data will be reviewed by the SMC if any of the following occur:

- Any SAE (regardless of the relationship to the study drug) throughout duration of study.
- 5 or more subjects in study (cumulative among all cohorts) experience a same grade 2 (or higher) related AE (laboratory or systemic) which is coded in the same high-level group term (HLGT) per MedDRA coding, throughout duration of study. Exception to this includes scenarios where there are obvious and acceptable physiological explanations for a Grade 2 or higher abnormality (e.g., Grade 3 hematuria in a menstruating female).
- Any subject experiences skin ulceration of any grade at an injection site.

8.7.2 Dose Escalation Halting Rules

Sentinel Subject Halting Rules

If any of the criterion below are met, the cohort will be suspended (enrollment and dosing), and the SMC ad hoc meeting will convene:

- Any SAE (regardless of the relationship to the study drug) through 48 hours post study drug administration.
- Any Grade 2 (or higher) adverse event deemed to be related to the study medication by the PI, having an initial onset within the first 72 hours post study drug administration that does not resolve within 72 hours from onset.
- Any subject experiences skin ulceration of any grade at an injection site.

Cohort Dose Escalation Halting Rules

If any of the criterion below are met, the escalation to the next cohort will be suspended (enrollment and dosing), and the SMC ad hoc meeting will convene.

- 2 or more subjects in a cohort experience the same grade 2 (or higher) related AE (laboratory or systemic) which is coded in the same HLGT per MedDRA coding, through Day 30 (SAD) or Day 30 (MAD) of the study.

- Two or more subjects within a cohort with post-dose QTcF > 500 or change from baseline >60 ms.
- Any subject experiences skin ulceration of any grade at an injection site.

8.7.3 Individual Halting Rules

If any of the criterion below are met, the subject will be discontinued from further dosing:

- Any SAE regardless of the relationship to the study drug, throughout the duration of the study.
- Any other condition that the Site PI judges to unduly increase the risk to the subject.
- Any subject experiences skin ulceration of any grade at an injection site. (Does not apply to infusion site).

8.7.4 Infusion Halting Rules (Part 3 for IV Dosing Only)

Infusion of study drug will be halted if any of the following manifestations of anaphylaxis develop and will not be restarted:

- Skin or mucous membrane manifestations: hives, moderate or severe pruritus, flushing, swollen joints, swollen lips, tongue or uvula.
- Respiratory compromise: dyspnea, wheezing, stridor.
- A decrease in systolic blood pressure to <90 mmHg or >30% decrease from baseline blood pressure or a decrease in diastolic blood pressure of >30% from baseline.
- 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.
- Confusion.

8.8 Safety Oversight (ISM and SMC)

8.8.1 Independent Safety Monitor

An ISM is a physician with relevant expertise whose primary responsibility is to provide to DMID an independent safety assessment in a timely fashion. This ISM is identified by the investigator site and approved by DMID. Participation is for the duration of the DMID study and is a voluntary position that does not receive payment. The ISM must meet the requirements of the NIAID conflict of interest policy.

The ISM:

- Is near the site and has the authority and ability to readily access subject records in real time.
- May be a member of the participating institution's staff but preferably be from a different organizational group within the institution.
- Should not be in a direct supervisory relationship with the PI.
- Should have no direct involvement in the conduct of this trial.

The ISM will:

- Sign a Conflict of Interest certification at the time they are asked to participate and provide updates to this information as needed.
- Receive reports of SAEs from the Site PI and will be notified by email when DMID is notified of the SAE.
- Evaluate the SAE and report their clinical assessment to DMID, through DMID-CROMS system organ classes (SOCS) in a timely manner using the attached report form and email the report to DMID-CROMS SOCS.
- Communicate with the Site PI as needed.
- Review additional safety related events at the request of DMID.
- Provide additional information to DMID by teleconference as requested.

8.8.2 Safety Monitoring Committee

This trial will utilize an SMC, an independent group of experts that advises DMID. The primary responsibility of the SMC is to monitor subject safety. The SMC is external to DMID and comprises at least 3 voting members. The SMC will consist of members with appropriate Phase 1 trial expertise to contribute to the interpretation of data from this trial. Its activities will be delineated in a SMC charter that will describe the membership, responsibilities, and the scope and frequency of data reviews. The SMC will operate on a conflict-free basis independently of the trial team. DMID or the SMC may convene ad hoc meetings of the SMC according to protocol criteria or if there are concerns that arise during this trial.

The SMC will review the safety data at the following timepoints:

- Organizational meeting (before starting this trial).
- Data review meeting, following completion of Part 1 and prior to Part 2 (MAD).
- Ad hoc meeting(s).
- Final review meeting, to be conducted 6-8 months after clinical database lock to review the cumulative unblinded safety data for this trial. Data will be provided in a standard summary format. The SMC may be asked to provide recommendations in response to questions posed by DMID.

All SMC reviews will be performed using unblinded data. Only blinded data will be presented during the open session. Study drug administration data, including dose interruptions, modifications, and the associated reason(s), will be reported to the SMC.

9 HUMAN SUBJECTS PROTECTION

9.1 Institutional Review Board/Independent Ethics Committee

The site principal investigator will obtain IRB approval for this protocol to be conducted at his research site and send supporting documentation to the DMID before initiating recruitment of subjects. The investigator will submit applicable information to the IRB/IEC on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6 GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Subjects), other federal, state, and local regulations. 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.

9.2 Informed Consent Process

Informed consent is a process that is initiated before an individual agrees to participate in a trial and continuing throughout a subject's participation in a trial. Before any trial 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 ICF. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

The Site PI or designee will describe the protocol to potential subjects face-to-face. The key information about the purpose of this trial, the procedures and experimental aspects of this trial, risks and discomforts, and any expected benefits to the subject will be presented first to the subject.

Subjects will also receive an explanation that this trial involves research, and a detailed summary of the proposed trial procedures and trial interventions/drugs. This will include aspects of this

trial that are experimental, the probability for random assignment to study drug groups, any expected benefits, all possible risks (including a statement that particular study drugs or procedures may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), and the expected duration of the subject's participation in this trial.

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 this 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 that there are no financial expenses to the subject for participating in this trial, as well as be informed of the anticipated prorated payments to the subject for participating in this trial. They will be informed of whom to contact (e.g., the Site PI) for answers to any questions relating to this trial.

Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in this trial may be terminated. The subjects will be informed that participation is voluntary and that they are free to withdraw from this trial for any reason at any time without penalty or loss of benefits to which they were otherwise entitled.

The extent of the confidentiality of the subjects' records will be defined, and subjects will be informed that applicable data protection legislation will be followed. Subjects will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written ICF, the subject is authorizing such access.

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 this trial are published, the subject's identity will remain confidential. Subjects will be informed whether confidential information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Subjects will be allowed sufficient time to consider participation in this trial and to discuss this trial with their family, friends, or legally authorized representative, or think about it before agreeing to participate.

ICFs will be IRB-approved and subjects will be asked to read and review the ICF. Subjects will sign the ICF before starting any trial procedures being done specifically for this trial.

Once signed, a copy of the ICF will be given to the subject(s) for their records. The subject(s) may withdraw consent at any time throughout the course of this trial. The rights and welfare of the subject(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this trial.

Trial personnel may employ recruitment efforts before obtaining trial consent if a patient-specific screening consent is on record or if the IRB has agreed that chart review is allowed without a fully executed screening consent. In cases where there is not a patient-specific screening consent on record, site clinical staff may pre-screen via chart review and refer potential subjects to the research staff. Research staff would obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

New information will be communicated by the Site PI or delegated staff to subjects who consent to participate in this trial in accordance with IRB requirements. The ICF will be updated and subjects will be re-consented per IRB requirements, if necessary. Subjects will be given a copy of all ICFs that they sign.

9.3 Consent for Future Use of Stored Specimens and Data

Residual clinical samples will be available upon the completion of the study; however, future use clinical samples may be requested from DMID and shipped from the DMID CMS at any time. These clinical samples will be shipped to and stored for up to 2 years at the Fisher Biorepository (DMID CMS).

The samples will not be sold or used directly for production of any commercial product. No human genetic tests will be performed on the samples. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject confidentiality. The recipients of specimens will be informed that these specimens have a NIH certificate of confidentiality.

There are no benefits to subjects in the collection, storage and subsequent use of their specimens for future research. Reports about future research done with subjects' samples will NOT be kept in their health records.

Subjects may be given the option to decide if they want their residual specimens to be used for future research or have these specimens destroyed at the end of this trial. The subject's decision can be changed at any time by notifying the study doctors or nurses in writing. However, if the subject originally consents to the future use of residual specimens and subsequently changes his/her decision, any data from a previously collected specimen may still be used for future research.

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

Children aged <18 years and elderly populations will be excluded from participation because insufficient data are available in adults to judge potential risk in children and elderly individuals, and as a Phase 1 trial in healthy subjects, there is no known benefit. For these same reasons, this trial will not include other special classes of subjects, such as fetuses, neonates, prisoners, institutionalized individuals, or others who may be considered vulnerable populations.

Neither women nor minorities will be excluded from participation in this trial. Women of child-bearing potential may be included as per the inclusion criteria (Section 5.1.1). Subjects will be recruited without regard to gender or race. It is expected that race will reflect that within the community.

9.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating PI's, their staff, and the Sponsor and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in this trial. No information concerning this trial, or the data generated from this trial will be released to any unauthorized third party without prior written approval of the DMID and the subject. Subject confidentiality will be maintained when trial results are published or discussed in conferences. The trial monitor or other authorized representatives of the Sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The CRU 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 non-clinical 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 US Government that is used for auditing or evaluation of federally funded projects, like this trial, 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 drug while participating 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 local IRB's policies and procedures, and subject to IRB approval.

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

10 STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) will be created prior to database lock. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures. Any deviation from the analysis outlined in the protocol will be described in the SAP.

For continuous variables, data will be summarized using descriptive statistics (such as sample size, mean, median, standard deviation, minimum, and maximum). For discrete variables, data will be summarized using frequencies and percentages.

10.1 Study Hypotheses

The objectives of this trial are to obtain safety, tolerability, and PK data for rezafungin. There are no formal hypotheses being tested in this trial.

10.2 Sample Size Considerations

No formal sample-size calculations based on testing a statistical hypothesis were constructed. There will be a total of 86 subjects in this three-part trial, 44 subjects in 6 cohorts will receive rezafungin or placebo via SC injection in Part 1/SAD, 32 subjects in 4 cohorts will receive rezafungin or placebo via SC injection in Part 2/MAD, and 10 subjects will receive rezafungin via both SC and IV injections in Part 3/BA. The number of subjects was selected to allow sufficient evaluation of safety, tolerability, and PK of the various dose regimens, and to be consistent with standards of practice for Phase 1 trials.

10.3 Treatment Assignment Procedures

10.3.1 Randomization Procedures

Each subject who completes the Screening assessment, meets all eligibility criteria, and is enrolled into this trial will randomized to rezafungin or placebo (Cohorts 1-10) or randomized to treatment sequence (Cohort 11),, except for replacement subjects. Replacement subjects will be assigned the same study drug dosing regimen as the replaced subject.

The randomization schedule will be generated centrally through AdvantageEDC^{SM} (Electronic Data Capture [EDC] System, Emmes) by the unblinded biostatistician, and a list will be transferred to the unblinded Site Pharmacist before the start of this trial as an emergency back-up. Part 1 Cohort 1 will have 4 subjects randomized 3:1 to receive rezafungin or placebo, respectively. There will be no sentinel dosing for Cohort 1. Within cohorts 2-6 in Part 1 and all cohorts of Part 2, 8 subjects will be randomized 3:1 to receive rezafungin or placebo, respectively. In each dosing cohorts 2-6 in Part 1 and all cohorts of Part 2, the first two subjects will be randomized 1:1 to receive rezafungin or placebo to ensure that one of the first two subjects receives rezafungin and the other placebo. The study drug assignment of the remaining subjects in each cohort will be randomly assigned in a 5:1 ratio of active drug to placebo to ensure the 3:1 ratio for the entire dosing cohort. In Part 3, 10 subjects will be randomized in a 1:1 ratio of dose route order (SC → IV or IV → SC). Enrollment will occur at one CRU.

Per ICH guideline E6: GCP, screening records that document why an individual was screened but not enrolled will be kept at the CRU. Reasons for screen failures will also be recorded in AdvantageEDC^{SM}.

Subjects will be enrolled online using the enrollment module of AdvantageEDC^{SM}. The randomization code will be prepared by statisticians at the SDCC and included in the enrollment module for this trial. AdvantageEDC^{SM} will assign each subject to a rezafungin or placebo group after demographic and eligibility data have been entered into the system. A designated individual at the CRU will be provided with a code list for emergency unblinding purposes, which will be kept in a secure place.

Instructions for using the enrollment module are included in the AdvantageEDC^{SM} User's Guide. Manual back-up procedures and instructions are provided for use in case the CRU temporarily loses access to the Internet or the online enrollment system is unavailable.

10.3.2 Masking Procedures

10.3.2.1 Blinding

For SAD and MAD subjects, the Site Pharmacist will be unblinded as to randomization assignment. Subjects, the PI, and CRU personnel other than the Site Pharmacist, the bioanalytical laboratory staff, and Fisher repository personnel will remain blinded to all randomization assignments. The PK analyst(s) will be unblinded. The DMID Medical Monitor, other NIAID personnel, and ICON personnel will remain blinded to all randomization

assignments. For subjects enrolled in Part 3 (Bioavailability), the subjects, the PI, and CRU personnel will be unblinded to randomization assignment.

Selected individuals not involved in conducting this trial, including members of the SMC, may have access to the unblinded data as needed for safety or other data review. The Site Pharmacist will remain unblinded during this trial.

10.3.3 Emergency Unblinding

Emergency unblinding of study drug assignment for a subject may be necessary due to a medical emergency, or any other significant medical event, if knowledge of the subject's study drug assignment impacts the subject's care. If an SAE or other circumstance requires the blind to be broken to ensure a subject's safety, the PI will immediately notify the DMID Medical Monitor if possible (within 24 hours) to discuss the case and reason for unblinding (a written narrative will follow within 48 hours of the event).

Procedures for emergency unblinding are detailed in the MOP for this trial.

10.4 Planned Interim Analyses

10.4.1 Interim Safety Review

An interim safety review will be performed upon completion of the SAD cohorts (1-6) and prior to starting the MAD and BA parts of the study.

An interim safety review will also be performed by the SMC upon completion of Day 30 for all subjects upon completion of the SAD cohorts (1-6) and prior to starting the MAD and BA parts of the study. This safety review may include but is not limited to enrollment, laboratory, and safety data. If criteria for halting the trial (as listed in Section 8.7) are met, an *ad hoc* SMC meeting will be held to review all available safety data and to make recommendations about the dosing of all further subjects in the trial. The SMC will receive data presented in aggregate (by cohort). Analysis by treatment assignment may be provided to the SMC in the closed session only.

10.4.2 Interim Immunogenicity or Efficacy Review

An interim PK analysis will be conducted upon the completion of the SAD cohorts (2-6).

All safety and PK data will be provided to the FDA for review prior to initiation of the MAD and BA portions of the trial. FDA will approve continued enrollment in the MAD and BA parts of the study and possibly recommend dose changes.

10.5 Final Analysis Plan

The safety analysis population will include all subjects that received any amount of study product and will be analyzed by treatment received. All subjects who receive a dose of rezafungin or placebo will be included in the safety analysis population. All subjects who receive a dose of rezafungin and have at least 1 measurable drug concentration after dosing in plasma will be included in the PK analysis population.

Placebo subjects may be pooled across multiple cohorts for analysis. The PK analysis population will include all subjects with at least one measurable rezafungin plasma concentration. Missing data will not be imputed. Details of study analyses for safety and PK data and their presentation will be fully described in the SAP, prepared by the SDCC and finalized prior to data lock.

10.5.1 Adverse and Serious Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities® (MedDRA). All AEs occurring after study drug dosing will be summarized using frequency counts and percentages. Summaries will be presented by dose cohort and control group. The following summaries will be presented for AEs and SAEs:

- Overall (i.e., regardless of severity or relationship to study drug,
- By severity grade (mild, moderate, or severe),
- By relationship to study drug,
- By MedDRA level hierarchy (system organ class, HLGT and preferred term).

Unless otherwise specified, at each level of subject summarization in reporting the incidence of the AEs, a subject will be counted once if the subject reported one or more AEs. If more than one occurrence of an AE is reported, the AE of the worst severity or the worst-case relationship assessment will be summarized. For crossover data, AEs will be summarized separately for each

treatment and the worst severity and worst-case relationship after each treatment will be summarized. An AE that began after the first treatment, continued into the second period, and worsened in severity after the second treatment will be considered a new AE associated with the second treatment.

10.5.2 Clinical Safety Labs, Vital Signs, and Electrocardiograms

Baseline for clinical safety labs, vital signs, and ECGs will be defined as the last result obtained before the dose of study product. For crossover data, there will be a separate baseline for each treatment. Changes from baseline for clinical safety labs, vital signs, and ECGs results will be summarized by dose group and time point. Clinical safety labs and vital signs will be graded (Appendix B) and summarized by severity, group, and visit. Rules for analyzing replicates for a safety time point (labs, vital signs, ECG), if obtained, will be described in the SAP.

Treatment-emergent abnormal laboratory test results will be identified. Treatment-emergent abnormal laboratory tests are tests for which the result was not graded as mild or worse at baseline but graded as mild or worse after dosing. Laboratory tests graded as mild at baseline, but moderate or worse any time after dosing will also be regarded as treatment-emergent abnormal laboratory test results.

ECG measurements will include heart rate, RR interval, QT interval, QTcF interval, PR interval, and QRS duration. Baseline for ECG measurements is defined per protocol as the value pre-dosing on Day 1 (or pre-dosing on Day 21 for period 2 of Part 3). Change from baseline will be summarized descriptively by regimen at each scheduled evaluation. QTc results will be summarized categorically according to the ICH Guideline E14 “Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs” (October 2005):

- QTcF >450 ms, males only
- QTcF >470 ms, females only
- QTcF >480 ms
- QTcF >500 ms
- QTcF increases from baseline by at least 30 ms but less than 60 ms
- QTcF increases from baseline by at least 60 ms

10.5.3 Additional Safety Analyses

Local reactogenicity at SC injection administration sites (Appendix B) will be summarized by type, toxicity grading, dose group, and time point. Skin ulcers at injection sites will be additionally summarized by size measurements and resolution. If there are multiple injection sites, the maximum severity across all injection sites will be summarized by day after injection at the respective sites.

10.5.4 PK Analysis Plan

PK profiles for rezafungin in plasma samples from all subjects who received at least one dose of rezafungin will be analysed for concentration of rezafungin (except Cohort 1) by a validated LC-MS/MS method. The following PK parameters will be estimated, by noncompartmental analysis methods using version 7.0 or higher of Phoenix WinNonlin®, for rezafungin concentrations in plasma.

C_{max}: The maximum concentration occurring at T_{max},

T_{max}: The time of maximum observed concentration sampled during a dosing interval,

AUC_{last}: The area under the curve (AUC) from the time of dosing to the last measurable concentration,

AUC extrapolated to infinity from the observed value of the last non-zero [or last quantifiable] concentration, ,

$AUC_{0\text{-}168}$: The AUC over the interval from time of first dose to 168 h after first dose (for Part 2 MAD only),

$t_{1/2}$: Terminal half-life,

λ_z: The first order rate constant associated with the terminal (log-linear) portion of the curve,

CL: The total body clearance for intravenous administration,

CL/F: The total body clearance for SC administration divided by the fraction of dose absorbed,

V_z: The volume of distribution associated with the terminal slope following IV administration

V_z/F: The volume of distribution associated with the terminal slope following SC administration divided by the fraction of dose absorbed,

F: The absolute BA will be calculated as the ratio of AUC_{inf} for the SC injection and the IV infusion of rezafungin administration (Part 3),

Dose proportionality for SAD and MAD in terms of C_{max} and AUC will be assessed using a power model,

AR: Drug observed accumulation ratio (Part 2)

Other PK parameters may be estimated as appropriate. Additional details for analysis of PK endpoints will be provided in the SAP.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The 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. The 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 QA reviews, audits, and evaluation of the trial 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 pharmacies, laboratories, and medico-technical departments involved in the clinical trial.

11.1 Compliance with Standards of Medical Research/Deviations

This protocol will be conducted in accordance with applicable ICH guidelines and GCP. Any instance of noncompliance with the protocol will result in a documented deviation. If a change is deemed necessary to protect the safety, rights or welfare of a subject, the Sponsor and IRB/IEC will be notified as soon as possible and preferably before introducing the deviation.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted Program Quality Management Plan (cQMP), the participating site and its subcontractors are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all study-related sites, 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 principal investigator 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 participating site(s) for clarification and resolution.

DMID-designated clinical monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, ICH/GCP guidelines, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to DMID.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after the completion of the study. In the event of an assessment, audit or inspection, the Investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified.

13 DATA HANDLING AND RECORD KEEPING

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.

Copies of the 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.

The sponsor and/or its designee will provide guidance to the site principal investigators and other study personnel on making corrections to the data collection forms and eCRF.

Training will be provided for the Electronic Data Capture (EDC) system. All personnel using the EDC system must have the appropriate education, training, and experience, or any combination thereof. The Investigator will be provided with standard operating procedures (SOPs) (contained in the SPM or a vendor-specific SOP) on the use of the EDC system. Documentation for employee education, training, and previous experience that pertains to the EDC system must be present in the Investigator files.

If electronic data systems other than those provided and maintained by the Sponsor are used for documentation and data capture, the Investigator must ensure that the systems are validated and ensure regular data back-up.

The eCRF will be signed by the Investigator or a Sub-Investigator listed on the FDA 1572 form. It is the responsibility of the Investigator to ensure the eCRFs are completed and submitted to the Sponsor (or designee) in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change, and person making change). At the completion of the study, the Sponsor will be provided with a final copy of each eCRF.

Management of clinical data will be performed in accordance with applicable Sponsor standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). Adverse events and concomitant medications will be coded using the MedDRA® and World Health Organization Drug (WHO DD) dictionaries respectively. Medical Electronic CRFs will be retained by the Sponsor and copies will be sent to the Investigator to maintain as the Investigator copy.

13.2 Data Management Responsibilities

Any source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure their accuracy and completeness. AEs must be recorded on the appropriate data collection form, assessed for severity and relationship, and reviewed by the site principal investigator or appropriate sub-investigator. AEs must be graded based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* September 2007, as modified for this study and as appropriate for the administration of rezafungin; see Appendix B.

Electronic data capture is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the PI must maintain complete and accurate documentation for the study.

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

The data coordinating center for this study, Emmes, 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, AEs, physical assessments, clinical laboratory values, and concomitant medications) will be entered into AdvantageEDC^{SM}, a 21 CFR Part 11-compliant EDC system managed by Emmes. AdvantageEDC^{SM} access is password protected. Access is granted to specific individuals based on the roles identified for this trial. The site enters the data into AdvantageEDC^{SM} from the DCFs completed by the study personnel. Data are validated through a query resolution process, comprising both automated and manual queries.

13.4 Types of Data

Data for this trial will include but are not limited to all data for safety and PK deemed necessary for the analysis per protocol, demographic data, ECG data, clinical laboratory values, concomitant medications, AEs, photographs, and medical history.

13.5 Study Records Retention

Trial documents will be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Site PI when these documents no longer need to be retained.

14 CLINICAL MONITORING

14.1 Site Monitoring Plan

Site monitoring is conducted to ensure that the human subject protections, trial and laboratory procedures, trial 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 Sponsor, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by DMID 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 site, trial personnel, and all trial documentation according to the DMID-approved site monitoring plan. Trial monitors will meet with Site PI to discuss any problems and actions to be taken and will document site visit findings and discussions.

15 PUBLICATION POLICY

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 (OER) 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. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

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, which will register the trial and post results.

The responsible party does not plan to request certification of delayed posting.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42CFR11
- NIH NOT-OD-16-149

16 LITERATURE REFERENCES

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17 APPENDICES

Appendix A. Schedules of Events

Table 11: Schedule of Study Procedures and Evaluations for Cohorts 1-6 in SAD (Part 1)

	Screening	Baseline Check-in	Inpatient – Confined to CRU							FU	Phone FU	FU/ ET	Unscheduled
Procedures/Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14 (±1)**	**21 (±1)**	**30 (±1)**	
Informed Consent Form[a]	X												
Assessment of Eligibility Criteria	X	X											
Demographics	X												
Height[b], Weight, BMI	X	X										X	
Review of Medical History	X	X											
Hepatitis and HIV tests[c]	X												
Follicle-stimulating hormone(FSH) test[d]	X												
Pregnancy test[e]	X	X										X	
Review of Concomitant Medications	X	X	X		X		X		X	X		X	X
Study drug randomization just prior to dosing[f]			X										
Administration of study drug[g]			X										
Vital signs[h]	X	X	X	X		X			X	X		X	X
Physical examination[i]	X	X	X	X		X			X			X	X
12-lead ECGs[j]	X		X						X			X	X
Blood for hematology & coagulation[k]	X	X		X					X			X	X
Blood for chemistry panel[k]	X	X		X					X			X	X
Urine for urinalysis, drug screen, alcohol[l]	X	X		X					X			X	X
Urine cotinine	X	X											

Procedures/Day	Screening	Baseline Check-in	Inpatient – Confined to CRU							FU	Phone FU	FU/ ET	Unscheduled
	-28 to -2	-1	1	2	3	4	5	6	7	14 (±1)	21 (±1)	30 (±1)	
Blood for PK analysis[m]			X	X	X		X		X	X		X	
Reactogenicity evaluation[n]			X	X	X	X	X	X	X	X	X	X	X
Assessment for AEs[o]			X	X	X	X	X	X	X	X	X	X	X
Counsel/reminders[p]	X								X	X	X	X	
Memory Aid[q]			X						X	X	X	X	X

Abbreviations: AE: adverse event; BMI: body mass index; CRU: clinical research unit; ECG: electrocardiogram; FU: follow-up; HIV: human immunodeficiency virus; PK: pharmacokinetic.

a. Informed consent will be obtained before initiating any trial-related assessments and procedures,
b. Height at Screening only,
c. Screen (serum) for hepatitis B surface antigen, hepatitis C virus antibody, and HIV antibody,
d. Perform FSH (serum) test in postmenopausal females only,
e. Perform serum pregnancy tests at Screening, Day -1, and Day 30 females only,
f. Randomize subjects on Day 1 just before dosing,
g. A single dose of study drug will be administered via SC injection on Day 1,
h. Vital signs will be obtained at Screening; on Day -1, on Day 1 prior to study drug administration (within 60 minutes prior to study drug) and at 15 minutes (±5 min), 1 hour (±10 min) and 2 hours(±10 min) post-dose; at 24, 72, 144 hours (±30 min), post-dose(Days 2, 4, and 7), and Days 14 (±1 day), and 30 (±1 day),
i. A complete PE will be performed at Screening and targeted PEs will be performed on Days -1, 1, 2, 4, 7, and 30 (±1 day),
j. ECGs will be obtained at Screening and on Day 1 within 60 minutes prior to study drug administration, and 4 hours (± 10 minutes) post-dose, Day 7, Day 30, and Unscheduled visits
k. Fasting (at least 8 hours) blood samples will be collected for hematology, coagulation and chemistries at Screening and on Days -1, 2, 7, and 30 (±1 day), Hematology tests consist of CBC with differential; coagulation tests consist of PT/PTT/INR; Chemistries panel includes albumin, glucose, blood urea nitrogen or urea, potassium, calcium, sodium, chloride, total protein, creatinine, CO2, CK, phosphorus, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin,
l. Urine will be collected for urinalysis, urine drug screen and urine alcohol at Screening and on Day -1. Urine will be collected for urinalysis on Days 2, 7, and 30 (±1 day),
m. Collect PK blood samples within 60 minutes before study drug dosing and at 0.5 (±5 min), 1, 2, 4, 6, 8, and 12 hours (±10 min),on (Day 1; 24 hours (±30 min) on Day 2; 48 hours (±30 min) on Day 3; 96 hours (±30 min) onDay 5; and 144 hours (±30 min) onDay 7 after dosing; and on Days 14 (±1 day) and 30 (±1 day), (No PK blood sample collection for Cohort 1)

n. Injection site assessment pre-dose and at 1 and 4 (± 10 min), 24, 48, 72, 96, 120, and 144 h (± 30 min) post dose, Day 14 (±1 day), Day 21 (±1 day), and Day 30 (±1 day). Unscheduled visits are not timed.
o. Subjects are to be assessed for AEs occurring from the time of the first dose of study drug through Day 30 (±1 day),

p. Counsel/reminder on contraceptive use and post-discharge instructions (dietary and medication/nonmedication vaccine and blood/blood product/sperm donation restrictions);as described in Section 5.1.
q. Memory Aid issued on Day 1, training on Day 7, and review on Days 14, 21, and 30 and at Unscheduled visits.

Table 12: Schedule of Study Procedures and Evaluations for Cohorts 7-10 in MAD (Part 2)

	Screening	Baseline Check-in	Inpatient – Confined to CRU							FU	FU/ ET	Unscheduled
Procedures/Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**30 (±1)**	**45 (±1)**	
			8	**9**	**10**	**11**	**12**	**13**	**14**			
			15	**16**	**17**	**18**	**19**	**20**	**21**			
Informed Consent Form[a]	X											
Assessment of Eligibility Criteria	X	X	X									
Demographics	X											
Height[b], Weight, BMI	X	X									X	X
Review of Medical History	X	X										
Hepatitis and HIV tests[c]	X											
Follicle-stimulating hormone (FSH) test[d]	X											
Pregnancy test[e]	X	X									X	
Review of Concomitant Medications	X	X	X		X		X		X	X	X	X
Study drug randomization just prior to dosing[f]			X									
Administration of study drug[g]			X									
Vital signs[h]	X	X	X	X		X			X	X	X	X
Physical examination[i]	X	X	X	X		X			X	X	X	X

Procedures/Day	Screening	Baseline Check-in	Inpatient – Confined to CRU							FU	FU/ ET	Unscheduled
	-28 to -2	-1	1	2	3	4	5	6	7	30 (±1)	45 (±1)	
			8	9	10	11	12	13	14			
			15	16	17	18	19	20	21			
12-lead ECGs[j]	X		X						X	X	X	X
Blood for hematology & coagulation[k]	X	X		X					X		X	X
Blood for chemistry panel[k]	X	X		X					X		X	X
Urine for urinalysis, drug screen, alcohol[l]	X	X		X					X		X	X
Urine cotinine	X	X										
Blood for PK analysis[m]			X	X	X		X		X	X	X	
Reactogenicity evaluation[n]			X	X	X	X	X	X	X	X	X	X
Assess for AEs[o]			X	X	X	X	X	X	X	X	X	X
Counsel/reminders[p]	X								X	X	X	
Memory Aid[q]			X						X	X	X	X

Abbreviations: AE: adverse event; BMI: body mass index; CRU: clinical research unit; ECG: electrocardiogram; FU: follow-up; HIV: human immunodeficiency virus; PK: pharmacokinetic.

a. Informed consent will be obtained before initiating any trial-related assessments and procedures,
b. Height at Screening only,
c. Screen (serum) for hepatitis B surface antigen, hepatitis C virus antibody, and HIV antibody,
d. Perform FSH (serum) test in postmenopausal females only,
e. Perform serum pregnancy tests at Screening, Day -1, and Day 45 females only,
f. Randomize subjects on Day 1 only,
g. A single dose of study drug will be administered via SC injection on Days 1, 8, and 15,
h. Vital signs will be obtained at Screening; on Day -1; on Day 1 within 60 minutes prior to study drug administration and at 15 minutes (±5 min), 1 hour (±10 min) and 2 hours (± 10 min) post-dose; and at 24, 72 and 144 hours (±30 min) post-dose on Days 2, 4, 7, 8, 9, 11, 14, 15, 16, 18, and 21; and on Days 30 (±1 day), and 45 (±1 day),
i. A complete PE will be performed at Screening and targeted PEs will be performed on Days -1, 1, 2, 4, 7, 8, 9, 11, 14, 15, 16, 18, 21, 30 (± 1 day), and 45 (±1 day),
j. ECGs will be obtained at Screening and on Day 1 within 30 minutes prior to study drug administration, and 4 hours (± 10 minutes) post-dose (Days 1, 8, and 15), Day 21, Day 30, Day 45, and Unscheduled visits
k. Fasting (at least 8 hours) blood samples will be collected for hematology, coagulation and chemistries at Screening and on Days -1, 2, 9, 16, 7, 14, 21 and 45 (±1 day). Hematology tests consist of CBC with differential; coagulation tests consist of PT/PTT/INR; Chemistries panel includes albumin, glucose, blood urea nitrogen or urea, potassium, calcium, sodium, chloride,

total protein, creatinine, CO2, CK, phosphorus, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin,

l. Urine will be collected for urinalysis, urine drug screen and urine alcohol at Screening, and on Day -1. Urine will be collected for urinalysis on Days 2, 7, 9, 14, 16, 21, and 45 (±1 day),
m. Blood for PK analysis (plasma) will be drawn pre-dose within 60 minutes before study drug dosing and at at 0.5 h (±5 min), 1 h (±10 min), 2 h (±10 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), and 12 h (±10 min),(Days 1 and 15); pre-dose within 15 minutes before study drug dosing and at 1 (±10 min), and 4 hours (±10 min), on Day 8; 24 hours (±30 min), on Days 2 and 16; 48 hours (±30 min) on Days 3 and 17; 96 hours (±30 min, on Days 5, 12, and 19; and 144 hours (±30 min) onDays 7, 14, and 21 after dosing; and on Days 30 (±1 day) and 45 (±1 day),
n. Injection site assessment pre-dose and at 1 and 4 (± 10 min), 24, 48, 72, 96, 120, and 144 h (± 30 min) post-dose, Day 30 (±1 day), and Day 45 (±1 day). Unscheduled visits are not timed.
o. Subjects are to be assessed for AEs occurring from the time of the first dose of study drug through Day 45 (±1 day),
p. Counsel/reminder on contraceptive use and post-discharge instructions (dietary and medication/nonmedication, vaccine and blood/blood product/sperm donation restrictions); as described in Section 5.1.
q. Memory Aid issued on Day 1, training on Day 7, and review on Days 30, 45 and at Unscheduled visits.

Table 13: Schedule of Study Procedures and Evaluations for Cohort 11 in BA (Part 3)

	Screening	**Baseline Check-in**	**Inpatient – Confined to CRU**							**FU**	**FU/ ET**	**Unscheduled**
Procedures/Day	**-28 to -2**	**-1 and 21**	**1** **22**	**2** **23**	**3** **24**	**4** **25**	**5** **26**	**6** **27**	**7** **28**	**14 and 35 (±1)**	**52 (±1)**	
Informed Consent Form[a]	X											
Assessment of Eligibility Criteria	X	X										
Demographics	X											
Height[b], Weight, BMI	X	X									X	
Review of Medical History	X	X										
Hepatitis and HIV tests[c]	X											
Follicle-stimulating hormone (FSH) test[d]	X											

Procedures/Day	Screening	Baseline Check-in	Inpatient – Confined to CRU							FU	FU/ ET	Unscheduled
	-28 to -2	-1 and 21	1	2	3	4	5	6	7	14 and 35 (±1)	52 (±1)	
			22	23	24	25	26	27	28			
Pregnancy test[e]	X	X									X	
Review of Concomitant Medications	X	X	X		X		X		X	X	X	X
Study drug randomization just prior to dosing[f]			X									
Administration of study drug[g]			X									
Vital signs[h]	X	X	X	X		X			X	X	X	X
Physical examination[i]	X	X	X	X		X			X	X	X	X
12-lead ECGs[j]	X		X								X	X
Blood for hematology & coagulation[k]	X	X		X					X		X	X
Blood for chemistry panel[k]	X	X		X					X		X	X
Urine for urinalysis, drug screen, alcohol[l]	X	X		X					X		X	X
Urine cotinine	X	X										
Blood for PK analysis[m]			X	X	X		X		X	X	X	X
Reactogenicity evaluation[n]			X	X	X	X	X	X	X	X		X
Assess for AEs[o]			X	X	X	X	X	X	X	X	X	X
Counsel/reminders[p]	X								X	X	X	X
Memory Aid[q]		X	X						X	X	X	X

Abbreviations: AE: adverse event; BMI: body mass index; CRU: clinical research unit; ECG: electrocardiogram; FU: follow-up; HIV: human immunodeficiency virus; PK: pharmacokinetic.

a. Informed consent will be obtained before initiating any trial-related assessments and procedures,
b. Height at Screening only,
c. Screen (serum) for hepatitis B surface antigen, hepatitis C virus antibody, and HIV antibody,
d. Perform FSH (serum) test for postmenopausal (females only),
e. Perform serum pregnancy tests at Screening Day -1 and Day 52 females only,
f. Randomize subjects on Day 1 only,
g. A single dose of study drug will be administered via SC injection/IV infusion on Days 1 and 22,

h. Vital signs will be obtained at Screening; on Day -1; on Days 1 and 22 within 60 minutes to study drug administration and at 15 minutes (±5 min), 1 and 2 hours (±10 min), post-dose; and on Days 2, 4, 7, 23, 25, 28 (±30 min) and 14 (±1 day), 35 (±1 day), and 52 (±1 day),
i. A complete PE will be performed at Screening and targeted PEs will be performed on Days -1, 1, 2, 4, 7, 14, 22, 23, 25, 28, 35, and 52. Days 14, 35, and 52 have (±1 day) window.
j. ECGs will be obtained at Screening and on Day 1 within 60 minutes prior to study drug administration, and 4 hours (± 10 minutes) post-dose (SC) and 1 hour (± 10 minutes) post-dose (IV) from start of infusion for IV admin, Day 52, and Unscheduled visits
k. Fasting (at least 8 hours) blood samples will be collected for hematology, coagulation and chemistries at Screening and on Days -1,2, 7, 23, 28, and 52 (±1 day), Hematology tests consist of CBC with differential; coagulation tests consist of PT/PTT/INR; Chemistries panel includes albumin, glucose, blood urea nitrogen or urea, potassium, calcium, sodium, chloride, total protein, creatinine, CO2, CK, phosphorus, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin,
l. Urine will be collected for urinalysis, urine drug screen and urine alcohol at Screening, and on Day -1. Urine will be collected for urinalysis on Days 2, 7, 23, 28, and 52 (±1 day),
m. Blood for PK analysis (plasma) will be drawn pre-dose within 60 minutes before study drug dosing and at 0.5(±5 min), 1, 2, 4, 6, 8, and 12 hours (±10 min) on Days 1 and 22; 24 hours (±30 min), on Days 2 and 23; 48 hours(±30 min) on Days 3 and 24; 96 hours (±30 min), on Days 5 and 26; and 144 hours (±30 min) on Days 7 and 28 after dosing; and on Days 14 and 35 (±1 day) and 52 (±1 day),
n. Injection site assessment pre-dose and at 1 and 4 (± 10 min), 24, 48, 72, 96, 120, and 144 h (± 30 min) post-dose, Day 14 (±1 day), and Day 35 (±1 day). Unscheduled visits are not timed.
o. Subjects are to be assessed for AEs occurring from the time of the first dose of study drug through Day 52 (±1 day),
p. Counsel/reminder on contraceptive use and post-discharge instructions (dietary and medication/nonmedication, vaccine and blood/blood product/sperm donation restrictions);as described in Section 5.1.
q. Memory Aid issued on Day 1, training on Day 7 (refresher on Day 28), reviewed on Days 21, 14, 35, 52 and at Unscheduled visits.

Appendix B. TOXICITY TABLE

Clinical Adverse Events			
VITAL SIGNS	**Mild** **(Grade 1)**	**Moderate** **(Grade 2)**	**Severe** **Grade 3**
Fever - °C	38.0-38.4	38.5-38.9	>38.9
Tachycardia - bpm	101-115	116-130	>130 or ventricular dysrhythmias
Bradycardia – bpm • Baseline ≥60 OR, if Baseline <60	• 50-54 OR, if Baseline <60, • 45-50	• 45-49 OR, if baseline <60, • 40-44	• <45 OR, if baseline <60 • <40
Hypertension (systolic) - mmHg	141-150	151-160	>160
Hypertension (diastolic) - mmHg	91-95	96-100	>100
Hypotension (systolic) - mmHg	85-89	80-84	<80
Tachypnea – breaths per min	23-25	26-30	>30
CARDIOVASCULAR	**Mild** **(Grade 1)**	**Moderate** **(Grade 2)**	**Severe** **(Grade 3)**
Arrhythmia		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)[1]	Asymptomatic, QTc interval 450-479 msec	Asymptomatic; QTc interval 480 to 499 msec OR Increase in interval 30-59 msec above baseline	Asymptomatic; QTc interval ≥ 500 msec OR Increase in interval ≥ 60 msec above baseline
PR Interval (prolonged)[1]	PR interval 0.21-0.25 sec	PR interval >0.25	Type II 2nd degree AV block OR Ventricular pause >3.0 sec
RESPIRATORY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Cough	Transient; no treatment	Persistent cough	Interferes with daily activities
Bronchospasm, Acute	Transient; no treatment; FEV1 71-80% 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
GASTROINTESTINAL	**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

[1]Inclusion dependent upon protocol requirements.

Diarrhea	2-3 loose or watery stools or <400 g/24 hours	4-5 loose or watery stools or 400-800 g/24 hours	≥6 loose or watery stools or >800g/24 hours OR requires IV hydration OR requires medical intervention
REACTOGENICITY			
LOCAL REACTIONS	**Mild** **(Grade 1)**	**Moderate** **(Grade 2)**	**Severe** **(Grade 3)**
Pain – experienced without touching the injection site (spontaneous discomfort)	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours OR interferes with activity	Any use of narcotic pain reliever OR prevents daily activity
Tenderness – hurts only when injection site is touched, or the arm is moved	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Pruritus (Itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema (Redness)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Induration (Hardness)/Swelling*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Nodule	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ulcer	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising)*	25 mm – 50 mm	51 mm – 100 mm	>100 mm

Erythema (Redness)*	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Induration (Hardness)/Swelling*	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Nodule	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Ulcer	1 mm – 50 mm	51 mm – 100 mm	>100 mm
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
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 AE (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

*Will not be used as halting criteria.

Laboratory and Vital Signs Reference Ranges, Eligibility Ranges, and Toxicity Grading

Laboratory Adverse Events*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Blood, Serum, or Plasma			
Sodium (hyponatremia) – mEq/L	131-132	129-130	<129
Sodium (hypernatremia) – mEq/L	144 – 145	146 – 147	>147
Potassium (hyperkalemia) – mEq/L	5.2 – 5.4	5.5 – 5.6	>5.6
Potassium (hypokalemia) – mEq/L	3.2-3.4	3.0 – 3.1	<3.0
Glucose (hypoglycemia) – mg/dL	65 – 69	55 – 64	<55
Glucose (hyperglycemia) – mg/dL Fasting	106 – 125	126 – 200	>200
Blood Urea Nitrogen – mg/dL	21-26	27 – 31	> 31
Creatinine (Male) – mg/dL	1.3 – 2.0	2.1-2.3	>2.3
Creatinine (Female) – mg/dL	1.0 – 1.7	1.8 – 2.0	>2.0
Calcium (hypocalcemia) – mg/dL	8 - <LLN	7.5 – 7.9	<7.5
Calcium (hypercalcemia) – mg/dL	ULN - 10.8	10.9 – 11.4	>11.4
CK-U/L	309-1000	1001-1500	>1500
Albumin (hypoalbuminemia) – g/dL	2.8 – 3.4	2.5 – 2.7	< 2.5
AST – U/L (Male)	40-97	98-195	>195
AST – U/L (Female)	32-77	78-155	>155
ALT – U/L (Male)	41-100	101-200	>200
ALT – U/L (Female)	33-80	81-160	>160

Laboratory Adverse Events*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Alkaline phosphatase – IU/L (Male)	131-260	261-390	>390
Alkaline phosphatase – IU/L (Female)	106-210	211-315	>315
Total Bilirubin (serum) – mg/dL	1.3-1.5	1.6-1.9	>1.9
Direct Bilirubin – mg/dL	NA	NA	NA
Chloride –mEq/L (hypochloremia)	NA	NA	NA
Chloride –mEq/L (hyperchloremia)	NA	NA	NA
CO2 –mEq/L (hypo)	NA	NA	NA
CO2 –mEq/L (hyper)	NA	NA	NA
Total Protein – g/dL	5.5 - 5.9	5.0 - 5.4	<5.0
Phosphorus- mg/dl (hypo)	2.3-2.4	2.1-2.2	<2.0
Phosphorus-mg/dl (hyper)	NA	NA	NA
Hemoglobin (Male) – g/dL	11.2 - 12.2	10.0 – 11.1	<10.0
Hemoglobin (Female) – g/dL	9.8 - 10.8	8.5 - 9.7	<8.5
WBC Increase – cell/mm^3	10,001– 15,000	15,001 – 20,000	> 20,000
WBC Increase – cell/mm^3 (African America Males)	9,001 – 14, 000	14,001 – 19, 000	>19,000
WBC Increase – cell/mm^3 (African American Females)	11,001 – 15,000	15,001 – 20,000	>20,000
WBC Decrease – cell/mm^3	2,500– 3,999	1,500 – 2,499	< 1,500
WBC Decrease – cell/mm^3 (African American Males)	2,200 – 2,499	1,200 – 2,199	<1,200
WBC Decrease – cell/mm^3 (African American Females)	2,200 – 2,499	1,500 – 2,199	<1,500

Laboratory Adverse Events*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Neutrophils Decrease – cell/mm^3	1,300 – 1,699	1,000 – 1,299	< 1,000
Neutrophils Decrease – cell/mm^3 (African American Males)	1,000 – 1,299	800 - 999	<800
Neutrophils Decrease – cell/mm^3 (African American Females)	1,100 – 1,299	1,000 – 1,099	<1,000
Platelets Decreased – 10^3/mm^3	120 – 149	100 – 119	<100
Hematocrit (Male) - %	33.0 -36.1	29.8 - 32.9	< 29.8
Hematocrit (Female) - %	29.5 - 32.6	26.0 – 29.4	< 26.0
RBC (Male) – x 10^6/uL	3.9 - 4.1	3.4 - 3.8	< 3.4
RBC (Female) – x 10^6/uL	3.5 - 3.7	3.0 - 3.4	< 3.0
Lymphocytes - cell/mm^3 decrease	600- 799	500 – 599	< 500
Monocytes – cell/mm^3 increase	1001-2000	2001-3000	>3000
Eosinophils - cell/mm^3 increase	871 - 950	951 - 1700	>1700
Basophils - cell/mm^3 increase	101 - 300	301 - 800	> 800
PT (prothrombin time) – seconds	11.6-12.6	12.7-13.7	>13.7
PT INR (Prothrombin INR)	1.2-1.4	1.5-1.9	2.0 or higher
PTT (partial thromboplastin time) –seconds	30.1-36.8	36.9-43.6	>43.6
Urine			
Protein	1+	2+	>2+
Glucose	1+	2+	>2+
Blood (microscopic) - red blood cells per high power field (rbc/hpf)**	3-10*	11-50*	>50 and/or gross blood**

Laboratory Adverse Events*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
*Abnormal laboratory values, performed as part of hematology, chemistry panel, or urinalysis but not listed in Appendix B, will be evaluated by the study clinicians, recorded in the source document and, if clinically significant, considered AEs and graded according to the criterion described in Section 8.1.			