Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Heald AE, Charleston JS, Iversen PL, et al. AVI-7288 for Marburg virus in nonhuman primates and humans. N Engl J Med 2015;373:339-48. DOI: 10.1056/NEJMoa1410345

Protocol Supplement

This supplement contains the following items:

Supplement to: Heald AE, Charleston JS, Iversen PL, et al. AVI-7288 for Marburg virus: bridging between nonhuman primates and humans. N Engl J Med 2015;373:339-48. DOI: 10.1056/NEJMoa1410345

CLINICAL STUDY PROTOCOL

DRUG:	AVI-7288
PROTOCOL NUMBER:	7288-us-101
PROTOCOL TITLE:	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers
IND NUMBER:	101,939
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street, Suite 7 Cambridge, MA 02142 USA Phone: (857) 242-3700
CURRENT VERSION (DATE)	06 (30 July 2013)
PRIOR VERSIONS (DATES)	05 (27 March 2013) 04 (31 January 2013) 03 (17 July 2012) 02 (14 June 2012) 01 (6 June 2012) 00 (30 March 2012)

CONFIDENTIALITY STATEMENT

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers
Study No:	7288-us-101
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This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) parts 11, 50, 54, 56, and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

A E Heald 31 July 2013

Alison E. Heald, MD
Senior Director, Clinical Development
Sarepta Therapeutics, Inc.
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Date

STUDY SYNOPSIS

NAME OF COMPANY	NAME OF FINISHED PRODUCT
Sarepta Therapeutics, Inc. 215 First Street, Suite 7 Cambridge, MA 02142 USA Phone: (857) 242-3700	AVI-7288 Drug Product **NAME OF ACTIVE INGREDIENT** AVI-7288

TITLE:

A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers

PROTOCOL NO.:

7288-us-101

INVESTIGATOR STUDY SITES:

This study will be conducted at 1 study center located in the United States.

OBJECTIVES:

- To evaluate the safety and tolerability of 14 once daily intravenous (IV) infusions of ascending doses of AVI-7288 compared to placebo in healthy male and female subjects
- To evaluate the pharmacokinetics (PK) of 14 once daily IV infusions of ascending doses of AVI-7288 in healthy male and female subjects

METHODOLOGY:

This is a Phase 1, randomized, double blind, placebo-controlled, multiple-dose, dose-escalation study to assess the safety, tolerability, and PK of AVI-7288 in healthy adult volunteers.

Up to 40 subjects will be randomized to 5 cohorts of 8 subjects each. Within each cohort, 6 subjects will receive AVI-7288 and 2 will receive placebo once daily for 14 days; subjects and study personnel will be blinded to treatment. Every effort will be made to include an equal number of male and female subjects in each cohort. Doses of AVI-7288 will be escalated in subsequent cohorts as follows: 1 mg/kg, 4 mg/kg, 8 mg/kg, 12 mg/kg, and 16 mg/kg. Cumulative safety data through Day 21 for each cohort will be reviewed by an independent Data Safety Monitoring Board (DSMB) prior to dosing of the next cohort.

All subjects will be confined to the study center from 1 day prior to the first dose of AVI-7288 or placebo until 48 hours after the last dose, i.e., from Day -1 (also referred to as check-in day) through Day 16. Subjects will return to the study center for safety evaluations 7 and 28 days post last dose on Days 21 and 42, respectively.

NUMBER OF SUBJECTS:

Approximately 130 subjects will be screened to allow 40 subjects to be randomized and dosed.

INCLUSION/EXCLUSION CRITERIA:

The study population for this Phase 1 multiple ascending dose study consists of healthy male and female subjects aged 18 to 50 years, inclusive, with a body mass index (BMI) of 18 to 35 kg/m^2, inclusive.

Inclusion Criteria:

A subject must meet all of the following criteria to be eligible for this study.

1. Man or woman 18 to 50 years of age, inclusive, at the time of screening.

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2. Body mass index 18 kg/m^2 to 35 kg/m^2, inclusive, at the time of screening and check-in (Day -1).

3. Good general health (e.g., no chronic health conditions such as hypertension, diabetes, chronic obstructive pulmonary disease, or cardiovascular disease) as determined by the Investigator. Subjects with mild seasonal allergies or benign conditions such as Gilbert's disease may be enrolled at the discretion of the Investigator.

4. Female subjects must be of non-childbearing potential or must, in conjunction with their sexual partner(s), use 2 forms of medically acceptable barrier contraception (e.g., a diaphragm with spermicidal jelly in conjunction with a male condom) during the screening period and for the entire duration of study participation including the 28-day follow-up. Non-childbearing potential is defined as postmenopausal documented by an elevated Follicle Stimulating Hormone (FSH) level or surgically sterile (e.g., tubal ligation, hysterectomy, and/or bilateral salpingo-oophorectomy).

5. Male subjects must either be sterile or agree to use, for the entire duration of the study and for 90 days post last dose, a male condom and the female sexual partner must also use a medically acceptable form of birth control (e.g. oral contraceptives).

6. Male subjects must agree to not donate sperm for at least 90 days after the last infusion of study medication.

7. Able to understand the requirements of the study, to provide written informed consent (as evidenced by signature on an informed consent document that is approved by an Institutional Review Board [IRB]), and agreeable to abiding by the study restrictions.

Exclusion Criteria:

A subject who meets any of the following criteria will be excluded from this study.

1. Pregnancy or breastfeeding.

2. A positive urine or blood screen for drugs of abuse, including alcohol.

3. Use of any tobacco- or nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to Check-in (Day -1).

4. A positive cotinine test indicating recent nicotine use.

5. Donated blood within 90 days or plasma within 30 days of first dose on Day 1.

6. Active substance abuse or any medical or psychiatric condition that could jeopardize the subject's safety or the subject's ability to comply with the protocol.

7. Use of any medications apart from vitamins, acetaminophen, or hormonal contraception within 14 days of first dose on Day 1. Subjects with mild seasonal allergies may use antihistamines at the discretion of the Investigator after approval by the Sponsor Medical Monitor.

8. Participation in any interventional clinical trial within 45 days of first dose on Day 1 (i.e., received any other investigational drug).

9. Recipient of an organ transplant (solid or hematopoietic).

10. Prolonged QT_cF interval > 440 ms for males or > 460 ms for females using the average of the triplicate

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electrocardiograms (ECGs) collected during screening, on Day -1, or just prior to dosing on Day 1.

11. Other clinically significant ECG abnormality, as determined by the Investigator.
12. Any clinically significant abnormal hematology, chemistry, coagulation, or urinalysis value, as determined by the Investigator.
13. Glomerular filtration rate (GFR) of < 90 mL/min, based on the Modification of Diet in Renal Disease (MDRD) equation.
14. Urine-albumin-to-creatinine ratio (UACR) > 30 mg/g.
15. Positive test for human immunodeficiency virus (HIV-1 serology) or known HIV infection.
16. Positive result for hepatitis B surface antigen (HBsAg) or for hepatitis C virus (HCV) antibody.
17. Use of alcohol-containing foods or beverages within 72 hours prior to check-in on Day -1.
18. Use of caffeine-containing foods or beverages within 24 hours prior to check-in on Day -1.
19. Febrile illness or significant infection within 48 hours before administration of the first dose of study drug on Day 1.

Note: Inclusion of each subject will be reviewed with a member of Sarepta Therapeutics Clinical Personnel prior to enrollment in the trial. Written approval from a member of Sarepta Therapeutics Clinical Personnel is required prior to randomization.

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

AVI-7288 is a phosphorodiamidate morpholino oligomer with positive charges (PMO*plus*™) that targets Marburg virus nucleoprotein (NP). AVI-7288 Drug Product is supplied in 5-mL vials containing 5 mL AVI-7288 at a concentration of 50 mg/mL. The dose levels of AVI-7288 for each cohort are:

- Cohort 1: AVI-7288 at 1 mg/kg IV
- Cohort 2: AVI-7288 at 4 mg/kg IV
- Cohort 3: AVI-7288 at 8 mg/kg IV
- Cohort 4: AVI-7288 at 12 mg/kg IV
- Cohort 5: AVI-7288 at 16 mg/kg IV

The amount of AVI-7288 Drug Product required to administer the required dose will be diluted to a volume of approximately 150 mL with normal saline solution (NSS) and given by IV infusion over 30 minutes once a day for 14 days. Infusions will be administered at approximately the same time each day.

REFERENCE TREATMENT:

Placebo control consists of approximately 150 mL NSS administered by IV infusion over 30 minutes once a day for 14 days. Infusions will be administered at approximately the same time each day.

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DURATION OF STUDY:

With a screening period of up to 21 days (including 1 day to check-in to the study unit), 14 days of dosing, and 28 days of safety follow-up post last dose, the study duration for each subject is expected to be approximately 63 days. As previously noted, subjects will be confined to a study unit for 17 of these days.

CRITERIA FOR EVALUATION:

Safety and Tolerability

Safety will be assessed through a review and evaluation of adverse events (AEs), serious adverse events (SAEs), AEs leading to study drug discontinuation, and serial clinical assessments including vital signs, physical examinations, clinical laboratory tests (hematology, chemistry and coagulation, urinalysis, standard urinary parameters, urinary biomarkers, serum cystatin C), and 12-lead ECGs. Additional safety assessments may be performed as deemed necessary by the Investigator.

Pharmacokinetics

The PK of AVI-7288 will be determined from multiple plasma and urine samples collected over 24 hours following the first administration of study drug on Day 1 and up to 48 hours following the final administration of study drug on Day 14. Trough levels will be measured on Days 2 through 14. The PK parameters to be characterized include the maximum plasma concentration (C_{max}), the apparent volume of distribution at steady state (V_{ss}), the elimination half-life ($t_{½}$), the time at which C_{max} occurs (T_{max}), area under the curve (AUC), total clearance at steady state (Cl_{ss}), mean residence time (MRT), and renal (i.e., urinary) clearance (Cl_R).

STATISTICAL METHODS:

Safety:

Safety and tolerability of AVI-7288 will be based upon the review of individual values and summary statistics. Incidence of treatment-emergent AEs will be tabulated by counts and percentages. Abnormalities in clinical laboratory, vital signs, and ECG will be based on pre-defined normal ranges and will be tabulated by dose group showing subject counts and percentages. Placebo-treated subjects will be pooled across all dose groups.

Pharmacokinetics:

Pharmacokinetic parameters will be summarized by mean, standard deviation (SD), coefficient of variation (CV), minimum, and maximum for each dose level. Dose proportionality for C_{max} and AUC(s) will be assessed visually by plotting these parameters against dose. Accumulation ratios for C_{max} and AUC(s) and time to steady state will be assessed. The PK profile following the last of 14 daily doses (Day 14 profile) will be compared to that following a single dose (Day 1 profile) to assess the within-subject impact of multiple dosing on the elimination of AVI-7288.

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
λ_z	elimination rate constant
Acc Ratio	accumulation for C_{max} and AUC
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the curve from 0 to 24 hours after dosing
$AUC\tau$	area under the curve over the dosing interval (24 hours)
AUC_{last}	area under the curve from time 0 to the time of the last quantifiable concentration
AUC_{∞}	area under the curve from time 0 to infinity
AUC_N	area under the curve (AUC_τ or AUC_∞) normalized by the dose
BQL	below quantification limit
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
$C_{avg,ss}$	average plasma concentration at steady-state
CL_R	urinary clearance
CL_{ss}	total clearance of drug at steady state
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration during a dosing interval at steady state
CS	clinically significant
C_{trough}	trough plasma concentration before dosing
CV	coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
eDCR	electronic data clarification request
FDA	United States Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate

GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HRPO	Human Research Protection Office
ICF	informed consent form
IND	investigational new drug application
IRB	Institutional Review Board
IV	intravenous
KIM-1	kidney injury molecule-1
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHF	Marburg hemorrhagic fever
mRNA	messenger RNA
MTD	maximum tolerated dose
MRT	mean residence time
NCS	not clinically significant
NOAEL	no-observed-adverse-effect level
NP	nucleoprotein
NSS	normal saline solution
ORP	Office of Research Protections
PFU	plaque forming unit
PHI	protected health information
PK	pharmacokinetic(s)
PMO	phosphorodiamidate morpholino oligomer
PMO*plus*™	phosphorodiamidate morpholino oligomer with positive charges
PT	prothrombin time
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event

$t_{½}$	elimination half-life
T_{max}	time at which C_{max} occurs
UACR	urine albumin-to-creatinine ratio
USAMRMC	US Army Medical Research and Materiel Command
V_{ss}	apparent volume of distribution at steady state
VP24	viral protein 24
VP40	viral protein 40
WBC	white blood cell

1 INTRODUCTION

Purpose of Study

The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of 14 once daily intravenous (IV) infusions of AVI-7288, a potential post-exposure prophylactic treatment for patients that have documented or suspected exposure to Marburg virus, compared to placebo. Four dose levels of AVI-7288 will be examined: 1, 4, 8, 12, and 16 mg/kg.

Marburg Hemorrhagic Fever

Marburg hemorrhagic fever (MHF) is a rare human disease caused by Marburg virus, a filamentous, single-stranded, negative-sense ribonucleic acid (RNA) virus of the family Filoviridae. The taxonomy of viruses within the genus *Marburgvirus* is shown in Table 1-1.

Table 1-1: Viruses within the Genus *Marburgvirus*

Family	*Filoviridae*	
Genus	*Marburgvirus*	
Species	*Marburg marburgvirus*	
Viruses	Marburg virus	Ravn virus

The vast majority of human infections have occurred in the context of outbreaks within central and southern Africa. MHF was first identified as the cause of a disease outbreak in Marburg, Germany in 1967, when several laboratory workers acquired the infection while processing organs from African green monkeys that had been imported from Uganda. Since then, the vast majority of human infection has occurred in the context of outbreaks within central and southern Africa; the few cases occurring outside of Africa have involved travel to or contact with that continent (Center for Disease Control and Prevention [CDC] 2010). There is only a single species of Marburg virus, Lake Victoria, of which there are 2 distinct lineages differing in amino acid sequence by approximately 22% (Knipe 2007).

Marburg virus infection is associated with a very high mortality rate. It may be transmitted to the host by way of exposure of mucosal surfaces or abraded skin to infected body fluids or through parenteral inoculation; the contribution of aerogenic transmission in the setting of natural epidemics is unknown. Death rates in the more sizeable MHF outbreaks have ranged from 23% to 88%, and of the 446 cases of MHF reported to date, 82.5% have been fatal (CDC 2010). Because it is highly lethal and readily transmitted from person to person, Marburg virus has been classified by the US CDC as a potential "Category A" agent of bioterrorism, and deemed of high priority for focused preparedness efforts, including the development of effective countermeasures to infection (CDC 2012).

Clinically, filovirus infections such as Marburg virus are characterized by the acute onset of illness after a typical incubation period of 4 to 10 days, with symptoms initially consisting of fever, chills, myalgia, and malaise. Disease features may evolve to encompass anorexia, nausea,

vomiting, abdominal pain, diarrhea, respiratory complaints, conjunctival injection, hypotension, edema, prostration, confusion, and coma. Hemorrhagic manifestations, coagulopathy, maculopapular rash, cytopenias, and increased transaminase levels may also be observed. In nonfatal cases, improvement typically commences at about 7 to 11 days; however, convalescence is protracted among survivors and may be associated with a number of complications, including myelitis, hepatitis, orchitis, and uveitis (Fauci 2008).

Currently there is no licensed vaccine or established effective therapy for Marburg virus or any other filovirus infection (Mandell 2009). Various experimental interventions including fusion inhibitors, transcription/replication inhibitors, maturation inhibitors, small interfering RNA, antibody therapy, inflammatory modifiers, and coagulation modulators have been preliminarily evaluated, but, in general, in vivo benefits have not been documented. Thus, there is a clear medical need for effective therapy and prophylaxis of Marburg virus infection.

AVI-7288

AVI-7288 is a phosphorodiamidate morpholino oligomer (PMO) capable of bearing positive charges (PMO*plus*™) that targets the viral messenger RNA (mRNA) encoding the Marburg virus nucleoprotein (NP), which is the major nucleoprotein involved in RNA encapsidation. The resultant nucleocapsid is thought to interact with membrane-associated viral protein 40 (VP40) in the viral budding and cellular extrusion process. The addition of the positive charges to the molecule is thought to nonspecifically enhance binding to negatively charged viral RNA, possibly subverting the consequences of individual viral resistance mutations if they should evolve.

AVI-7288 consists of 23 bases and contains 5 positively charged piperazinyl moieties. Its chemical name is:

> RNA, (P-deoxy) (2',3'-dideoxy-2',3'-imino-2',3'-seco) (2'a-5') (**G**-P-(dimethylamino)-**A** - P-(dimethylamino)-**A** – P-(dimethylamino)– **m^{5}U** - P-(dimethylamino)-**A** - P-(dimethylamino)– **m^{5}U** - P-(dimethylamino)– **m^{5}U** - P-(dimethylamino)-**A** - P-(dimethylamino)-**A** - P-(dimethylamino)–**C** - P-(1-piperazinyl)–**A** - P-(dimethylamino)-**I** - P-(1-piperazinyl)–**A** - P-(dimethylamino)–**C** - P-(1-piperazinyl)– **m^{5}U** - P-(dimethylamino)–**G** - P-(dimethylamino)–**A** - P-(dimethylamino)–**C**- P-(1-piperazinyl)–**A** - P-(1-piperazinyl)–**A** - P-(dimethylamino)–**G** - P-(dimethylamino)– **m^{5}U** -P -(dimethylamino)–**C**), 5'-[P-[4-[[2-[2-(2-hydroxyethoxy)ethoxy] ethoxy]carbonyl]-1-piperazinyl]-N,N-dimethylphosponamidate.

To date, AVI-7288 has been evaluated in clinical and nonclinical studies as a component of AVI-6003, which entails the administration of AVI-7288 and AVI-7287, a similar PMO*plus* that targets Marburg virus viral protein 24 (VP24). This is because initial nonclinical studies in mouse and guinea pig lethal challenge models suggested that AVI-6003 was the best candidate for post-exposure prophylaxis of Marburg virus. However, subsequent studies in a cynomolgus macaque Marburg virus lethal challenge model demonstrated that AVI-7288 is the only active component in AVI-6003. Therefore, Sarepta Therapeutics amended the Investigational New Drug Application (IND) to remove AVI-7287 from the development plan and to focus on AVI-7288 as a single oligomer candidate for development.

AVI-7288 is being developed for administration as post-exposure prophylaxis following documented or suspected exposure to Marburg virus. In general, the development plan will seek to identify and confirm an effective and well-tolerated dose in an appropriate animal challenge model and will attempt to replicate systemic exposures in healthy human volunteers that are comparable to those that afford protection in the experimental model.

Nonclinical Experience with AVI-7288

Support for the efficacy of AVI-7288 derives from studies in mouse, guinea pig, and nonhuman primate lethal challenge models performed at the United States Army Medical Research Institute for Infectious Diseases. In these studies, treatment with AVI-7288 or AVI-6003 (AVI-7287 and AVI-7288 in a 1:1 ratio) significantly increased survival in mice, guinea pigs, and nonhuman primates exposed to Marburg virus. As the mouse and guinea pig studies utilized a species-adapted strain of Marburg virus, and as the nonhuman primate model of Marburg virus most closely mimics the course of the disease in humans, the most relevant information for human efficacy derives from nonhuman primate studies.

In the 5 such studies conducted to date, a total of 61 cynomolgus macaques were challenged with lethal viral inoculums (approximately 1000 plaque forming units [pfu]/monkey) of Marburg virus (Musoke variant) followed by up to 15 daily doses of AVI-7288 (alone or as part of AVI-6003) (n=58) or placebo or scramble control (n=13). At 28 or 40 days post-infection, 48 of the 58 (82.7%) animals treated with AVI-7288 (alone or as part of AVI-6003) had survived versus none of the placebo-treated animals. The efficacy of AVI-7288 appeared dose dependent: survival rates in animals treated with 3.75 or 7.5 mg/kg of AVI-7288 (administered by IV bolus as part of AVI-6003 doses totaling 7.5 or 15 mg/kg, respectively) showed 60% survival rates, whereas animals treated with 15 mg/kg AVI-7288 (administered by IV bolus alone or as part of a 30 mg/kg dose of AVI-6003) showed survival rates of 92%. As the 15 mg/kg dose of AVI-7288 was the most effective dose tested, it is currently considered the target dose for use in humans.

AVI-6003 was generally well tolerated in 2 separate 28-day, repeat-dose toxicology studies conducted in rat (at doses of 8 to 400 mg/kg/day) and cynomolgus monkeys (4 to 200 mg/kg/day). In both studies, the kidney was identified as the most sensitive organ, with the rat appearing to be the more sensitive species. There were no clear test article-related findings for ophthalmoscopic examinations, hematology or coagulation evaluations, or organ weight evaluations in either species; however, dose-dependent effects on the kidney including proximal tubular degeneration/necrosis and basophilic granules in tubular cells were observed in both. Of note, the kidney findings were partially recovered by 14 days post last dose in the rat and 30 days post last dose in the monkey, suggesting reversibility. In a subsequent study in which rats administered 15 daily doses of 1.5, 3, 15, or 30 mg/kg AVI-6003 were necropsied on Day 16 or 1, 3 or 6 months post last dose, the adverse kidney effects (minimal to mild tubular degeneration/necrosis) observed in the 2 highest dose levels were reversible at the 1-month recovery period, while the incidental kidney findings (basophilic granules in the proximal tubular cells) observed at all dose levels were completely reversible at the 6-month recovery period. These findings indicate that AVI-6003's effects on the kidney, which most likely reflect accumulation of drug as part of the elimination process, are completely reversible following cessation of treatment.

Preliminary results are available from a PK/pharmacodynamic study of AVI-7288 (7288-pkd-001) in which AVI-7288 at doses of 3.75, 7.5 and 15 mg/kg/d were administered IV to cynomolgus macaques, uninfected and infected with Marburg Musoke 1000 pfu/monkey by subcutaneous injection. Survival in infected animals administered AVI-7288 3.75, 7.5 and 15 mg/kg/d for 14 days was 0/6 (0%), 2/6 (33%) and 5/6 (83%), respectively. The area under the curve (AUC) and maximum plasma concentration (C_{max}) over time were comparable in both infected and uninfected animals, suggesting that the disease course does not alter the PK of AVI-7288.

The exception to the above generalization is one male animal in the 15 mg/kg/d dose group that succumbed to HFV infection on day 10. The AUC_{0-24} for that animal on day 9 was 457,390 ng*hr/mL compared to the two other males in this dose group with a mean AUC_{0-24} of 74,029 ng*hr/mL. Animals dying from HFV generally experience multiple organ failure, including kidney failure, which likely results in increased AUC, as the kidney is the primary route of excretion for AVI-7288. Interpretation of the results from this animal is further confounded by the finding during necropsy that the indwelling catheter, although centrally present, had become explanted from the vena cava during the study execution. The gross findings included mediastinal fluid accumulation, inconsistent with HFV infection, which may have served as a depot reservoir for AVI-7288, further increasing the AUC.

Further details regarding nonclinical experience with AVI-6003 and AVI-7288 are provided in the Investigator's Brochure.

Clinical Experience with AVI-7288

To date, only 1 clinical study has been conducted with AVI-6003, and none have been conducted with AVI-7288 alone. Protocol 6003-us-101, a first-in-human, double-blind, placebo-controlled, single ascending dose study of AVI-6003, was completed in November 2011. A total of 30 subjects, 16 males and 14 females ranging in age from 18 to 49 years, were randomized to 1 of 6 dose escalation cohorts (0.01, 0.1, 1, 3, 6 and 9 mg/kg) of 5 subjects each. Subjects in each cohort received a single IV infusion of AVI-6003 or matching placebo in a 4:1 ratio and were followed for 28 days. The dose of AVI-7288 consisted of one-half the total dose of AVI-6003 for each cohort (e.g., 0.005, 0.05, 0.5, 1.5, 3, and 4.5 mg/kg).

AVI-6003 was safe and well tolerated at all doses studied. All subjects completed the 28-day study except for 1 who was randomized to the 0.1 mg/kg cohort, had a history of schizophrenia, and withdrew consent following an exacerbation of this illness (assessed as an SAE). Approximately half (54.2%) of the AVI-6003-treated subjects experienced a total of 27 treatment-emergent adverse events (TEAEs), of which only 6 (20.8%) were assessed as related to study treatment. All treatment-related TEAEs were mild in severity and, except for headache, which was reported by 2 subjects, none was reported by more than 1 subject. There were no SAEs other than exacerbation of schizophrenia in the 1 subject noted above, nor were there any discontinuations due study treatment or deaths. There were no clinically significant or dose-dependent effects of AVI-6003 on any of the safety endpoints including clinical laboratory assessments (hematology, coagulation, chemistry, urinalysis, reticulocyte counts, and complement levels), vital signs, electrocardiograms (ECGs), physical examinations, pulse

oximetry, and cardiac telemetry, nor were any gross abnormalities in fluid status, nephrotoxicity, changes in renal function, or changes in biomarkers of renal dysfunction observed.

Pharmacokinetic analyses of both components of AVI-6003 (i.e., AVI-7287 and AVI-7288) indicated that plasma profiles at the higher dose levels plateaued at the last 3 to 4 time points. For AVI-7287, C_{max} at the lowest and highest doses of 0.01 and 9 mg/kg (0.005 and 4.5 mg/kg for each component) averaged 34.1 and 23,300 ng/mL, respectively, and for AVI-7288, it averaged 36.4 and 26,900 ng/mL, respectively. Systemic clearance was similar for both components: for AVI-7287, it averaged 93.6 mL/hr/kg at 0.01 mg/kg and 123 mL/hr/kg at 9 mg/kg; and for AVI-7288, it averaged 104 and 136 mL/hr/kg, respectively. Volume of distribution (V_{ss}) was also similar across the 2 components: for AVI-7287, it averaged 189 mL/hr at 0.01 mg/kg and 537 at 9 mg/kg; and for AVI-7288, it averaged 158 and 569 mL/hr, respectively. Elimination half-life was about 2 to 5 hours for both components.

1.1 Summary of Potential Risks

Foreseeable risks to participants in the present study include those related to study drug and those related to study procedures. As noted above, no drug-related safety issues were identified in the single ascending dose study 6003-us-101, in which healthy subjects received a single dose of AVI-6003 (which included sequential infusions of AVI-7287 and AVI-7288 in a 1:1 fixed-dose ratio) at total doses of up to 9 mg/kg. However, reversible effects of AVI-6003 on kidney have been observed in preclinical studies (refer to Section 1 and the Investigator's Brochure for additional details); therefore heightened renal monitoring is included as part of this study.

Foreseeable risks associated with venipuncture include bruising, local pain, swelling, scarring at site, vasovagal syncope, and infection. Measures taken to minimize these risks include performance by trained medical personnel using aseptic techniques. Potential risks associated with ECG include skin irritation. Additional risks associated with laboratory analyses and ECGs include discovery of a previously undetected, significant abnormality. If any significant abnormality is discovered, the subject will be notified and follow-up care with a primary physician or other health care provider will be recommended.

Although not observed in animal studies or the single ascending dose study in humans, subjects could experience systemic allergic reactions including symptoms such as rash, fever, chills, difficulty breathing, swelling of the face, lips or tongue, seizure or loss of consciousness. Subjects could also experience local reactions to IV administration, including redness, pain, itching, burning, or sensitivity reactions (headache, fever, nausea, welts) due to use of heparin post-dose to flush the line. To mitigate such risks, all subjects will be monitored closely in an inpatient unit during the 14-day dosing period and for 48 hours after completion of the last dose of study drug. Medical emergency equipment will be available at the clinic.

Additional measures to minimize risk to participants include review of clinical safety and laboratory results by an independent Data Safety Monitoring Board (DSMB) on an ad hoc basis and prior to dose escalation as well as pre-specified stopping rules, as detailed in Section 5.2.3.

1.2 Summary of Potential Benefits

This trial is designed to characterize the safety, tolerability, and PK of multiple IV doses of AVI-7288 in healthy human volunteers. Subjects enrolled in the trial are not expected to receive any medical benefit from their participation.

2 STUDY OBJECTIVES

- To evaluate the safety and tolerability of 14 once-daily IV infusions of ascending doses of AVI-7288 compared to placebo in healthy male and female subjects

- To evaluate the PK of 14 once-daily IV infusions of ascending doses of AVI-7288 in healthy male and female subjects

3 INVESTIGATIONAL PLAN

3.1 Endpoints

3.1.1 Efficacy Endpoints

Efficacy will not be assessed in this Phase 1 study.

3.1.2 Safety Endpoints

The safety and tolerability of AVI-7288 will be assessed through a review and evaluation of:

- The frequency and severity of AEs, SAEs, and discontinuations due to AEs
- Laboratory testing including hematology, coagulation, chemistry, urinalysis, standard urinary parameters, urinary biomarkers, and serum cystatin C
- Estimated GFR, based on the Modification of Diet in Renal Disease (MDRD) equation
- Cardiac function as measured by 12-lead ECG
- Vital signs
- Physical examinations

3.1.3 Pharmacokinetic Endpoints

Pharmacokinetic parameters to be estimated from plasma concentration-time data, using actual sampling times, include:

C_{max} observed maximum plasma concentration (ng/mL)

T_{max} time to reach the observed maximum plasma concentration (hr)

$AUC\tau$ area under the curve calculated using the trapezoidal method over the dosing interval (24 hours) (ng*hr/mL)

AUC_{last} area under curve from time 0 to the time of the last quantifiable concentration C_{last} (ng*hr/mL)

AUC_{∞} area under the curve from time 0 to infinity, calculated according to the following equation $AUC = AUC_{last} + C_{last} / \lambda_z$ (ng*hr/mL)

AUC_{∞} will be reported if $t_{1/2,\lambda}$ is calculable and if C_{last} / λ_z represented 30% or less of the AUC value. AUC values where C_{last} / λ_z is less than 30% but equal to or greater than 20 % of the AUC value will be flagged in the report.

MRT_{∞}	mean residence time, calculated as $AUMC_{\infty}/AUC_{\infty}$
AUC_N	area under the time curve ($AUC\tau$ or AUC_{∞}) normalized by the dose
$\%AUC_{\infty,ex}$	percentage of AUC_{∞} obtained by extrapolation, calculated by the following equation: $\frac{AUC_{\infty} - AUC_{last}}{AUC_{\infty}} * 100$
$t_{1/2,\lambda}$	elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$
λ_z	first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve
$C_{max,ss}$	maximum plasma concentration during a dosing interval at steady state
C_{trough}	trough plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose
Swing (%)	$[(C_{max}-C_{min})/C_{min}]*100$
$C_{avg,ss}$	average plasma concentration at steady-state, calculated as $AUC\tau/\tau$
CL_{ss}	total clearance of drug at steady state
V_{ss}	apparent volume of distribution at steady-state, calculated as $MRT_{\infty}*CL_{ss}$
Acc Ratio	accumulation for C_{max} and AUC estimated by dividing the PK parameter on Day 14 by the same parameter on Day 1

In addition, the following PK parameters will be calculated from the urine levels of AVI-7288 treated subjects:

- Amount excreted for each defined urine collection time point
- Cumulative amount excreted over time (up to 1 day after last administration)
- Cumulative percentage of injected AVI-7288 excreted in the urine
- Calculated Cl_R (i.e., urinary clearance).

3.2 Study Design

This is a Phase 1, randomized, double blind, placebo-controlled, multiple-dose, dose-escalation study to assess the safety, tolerability, and PK of AVI-7288 in healthy adult volunteers.

Up to 40 subjects will be randomized to 5 cohorts of 8 subjects each. Within each cohort, 6 subjects will receive AVI-7288 and 2 will receive placebo once daily for 14 days. Every effort will be made to include an equal number of male and female subjects in each cohort. The dose of AVI-7288 will be escalated in each sequential cohort as follows: 1 mg/kg, 4 mg/kg, 8 mg/kg, 12 mg/kg, and 16 mg/kg. Cumulative safety data through Day 21 for each cohort will be reviewed by an independent DSMB prior to dosing of the next dose cohort.

All subjects will be confined to the study center from 1 day prior to the first dose of blinded study drug (AVI-7288 or placebo) until 48 hours after the last dose, i.e., from Days -1 through 16. Subjects will return to the study center for safety evaluations 7 and 28 days post-last dose on Days 21 and 42, respectively.

3.2.1 Completion of a Subject's Participation in the Study and Overall Study Completion

3.2.1.1 Completion of a Subject's Participation in the Study

The length of a subject's participation will be from the time the informed consent form is signed until completion of the Day 42 assessments. A subject will be considered "completed" when the subject has completed the Day 42 assessments.

3.2.1.2 Premature Subject Discontinuation from the Study

Subjects are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further treatment or penalty or loss of benefits to which the volunteer is otherwise entitled. A subject's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor.

Subjects who receive at least 1 dose of investigational product and who are withdrawn from the study during the 14-day dosing period will be encouraged to remain in the study unit for 48 hours after their last dose of study drug to collect the discharge evaluations (same as Day 16 evaluations) and to return for the Day 21 and Day 42 outpatient visits. Subjects who are withdrawn from the study after the 14-day dosing period will be asked to complete all early termination assessments (same as Day 42 assessments) as soon as possible. Moreover, every reasonable effort should be made to determine the reason for a subject's decision to withdraw from the study and the importance of continuing safety follow-up through Day 42 should be stressed. If applicable, at least 3 attempts should be made to contact the subject either by telephone, electronic mail, or registered mail.

Post-study SAEs will be reported according to Section 7.3.4.

At the end of the subject's participation in the study, the Investigator will document the reason(s) for study discontinuation on the appropriate screen/form of the electronic case report form (eCRF). As specified in Section 5.4, subjects who are withdrawn from the study after receiving their first dose of study drug will not be replaced.

3.2.1.3 Overall Study Completion

The study will be considered to be complete when the last dosed subject has completed his/her Day 42 assessments (including early termination assessments) or is withdrawn from the study or is considered lost to follow-up.

3.3 Discussion of Study Design

This study will assess the safety and tolerability and PK profile of repeat doses of AVI-7288 in healthy adult volunteers. In particular, the renal safety of AVI-7288 will be closely evaluated with both standard and newer, more sensitive biomarkers of renal function, including urinary kidney injury molecule-1 (KIM-1) and urinary cystatic C. Monitoring of GFR and evaluation serum cystatin C levels will also be performed at regular intervals. Pharmacokinetic data from this and any ensuing human study will be critical for confirming that a selected dose produces exposures in humans comparable to those shown to be effective in nonhuman primate lethal challenge studies, and thus would be reasonably likely to confer protection from lethal infection in humans.

A staggered dosing scheme, which allows escalation of dose to the next dose level only if no significant safety concerns are identified in the prior dose cohort, has been adopted to mitigate potential risk to the subjects. During regular evaluations of clinical, laboratory, and AE data, the DSMB may identify a potential safety signal for AVI-7288 that could lead to study termination or other changes in the protocol including lowering or repeating a dose level. Overall, these safeguards provide a strategy that will minimize any safety concerns associated with this experimental study drug.

Randomization will be used to avoid bias in the assignment of subjects to AVI-7288 or placebo, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across the assigned treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Blinded treatment (AVI-7288 versus placebo) will be used to reduce potential bias during data collection and evaluation of clinical (safety) parameters.

4 SUBJECT POPULATION AND SELECTION

The study population for this Phase 1 multiple ascending dose study consists of healthy male and female subjects aged 18 to 50 years, inclusive, with a body mass index (BMI) of 18 to 35 kg/m^2, inclusive.

4.1 Inclusion Criteria

A subject must meet all of the following criteria to be eligible for this study.

1. Man or woman 18 to 50 years of age, inclusive, at the time of screening.

2. Body mass index 18 kg/m2 to 35 kg/m2, inclusive, at the time of screening and check-in (Day -1).

3. Good general health (e.g., no chronic health conditions, such as hypertension, diabetes, chronic obstructive pulmonary disease, or cardiovascular disease) as determined by the Investigator. Subjects with mild seasonal allergies or benign conditions such as Gilbert's disease may be enrolled at the discretion of the Investigator.

4. Female subjects must be of non-childbearing potential or must, in conjunction with their sexual partner(s), use 2 forms of medically acceptable barrier contraception (e.g., a diaphragm with spermicidal jelly in conjunction with a male condom) during the screening period and for the entire duration of study participation including the 28 day follow-up. Non-childbearing potential is defined as postmenopausal documented by an elevated Follicle Stimulating Hormone (FSH) level or surgically sterile (e.g., tubal ligation, hysterectomy, and/or bilateral salpingo-oophorectomy).

5. Male subjects must either be sterile or agree to use, for the entire duration of the study and for 90 days post last dose, a male condom and the female sexual partner must also use a medically acceptable form of birth control (e.g. oral contraceptives).

6. Male subjects must agree to not donate sperm for at least 90 days after the last infusion of study medication.

7. Able to understand the requirements of the study, to provide written informed consent (as evidenced by signature on an informed consent document that is approved by an Institutional Review Board [IRB]), and agreeable to abiding by the study restrictions.

4.2 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from this study.

1. Pregnancy or breastfeeding.

2. A positive urine or blood screen for drugs of abuse, including alcohol.

3. Use of any tobacco- or nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to check-in (Day -1).

4. A positive cotinine test indicating recent nicotine use.

5. Donated blood within 90 days or plasma within 30 days of first dose on Day 1.

6. Active substance abuse or any medical or psychiatric condition that could jeopardize the subject's safety or the subject's ability to comply with the protocol.

7. Use of any medications apart from vitamins, acetaminophen, or hormonal contraception within 14 days of first dose on Day 1. Subjects with mild seasonal allergies may use antihistamines at the discretion of the Investigator after approval by the Sponsor Medical Monitor.

8. Participation in any interventional clinical trial within 45 days of first dose on Day 1 (i.e., received any other investigational drug).

9. Recipient of an organ transplant (solid or hematopoietic).

10. Prolonged QTcF interval > 440 ms for males or > 460 ms for females using the average of the triplicate ECGs collected during screening, on Day -1, or just prior to dosing on Day 1.

11. Other clinically significant ECG abnormality, as determined by the Investigator.

12. Any clinically significant abnormal hematology, chemistry, coagulation, or urinalysis value, as determined by the Investigator.

13. Glomerular filtration rate (GFR) of < 90 mL/min, based on the Modification of Diet in Renal Disease equation.

14. Urine-albumin-to-creatinine ratio (UACR) > 30 mg/g.

15. Positive test for human immunodeficiency virus (HIV-1 serology) or known HIV infection.

16. Positive result for hepatitis B surface antigen (HBsAg) or for hepatitis C virus (HCV) antibody.

17. Use of alcohol-containing foods or beverages within 72 hours prior to check-in on Day -1.

18. Use of caffeine-containing foods or beverages within 24 hours prior to check-in on Day -1.

19. Febrile illness or significant infection within 48 hours before administration of the first dose of study drug on Day 1.

Note: Inclusion of each subject will be reviewed with a member of Sarepta Therapeutics Clinical Personnel prior to enrollment in the trial. Written approval from a member of Sarepta Therapeutics Clinical Personnel is required prior to randomization.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Test Article

Active drug consists of AVI-7288 formulated with phosphate buffered saline at a concentration of 50 mg/mL. AVI-7288 Drug Product is supplied in aseptically filled, 5-mL vials containing 5 mL AVI-7288. It is a concentrate intended for dilution in normal saline solution (NSS) followed by IV administration.

5.1.2 Reference Treatment

A 150-mL NSS infusion bag will be labeled appropriately and used for the placebo control.

5.1.3 Packaging and Labeling

The label text for AVI-7288 Drug Product will comply with Good Manufacturing Practice (GMP) and other applicable regulatory requirements and will minimally include the protocol number ("AVI-us-7288"), contents of the vial ("AVI-7288 Drug Product"), the appropriate cautionary statements per 21 CFR 312.6, concentration (50 mg/mL), lot number (or alternative code), storage conditions, retest date, and the name of the Sponsor/manufacturer.

5.1.4 Storage

Vials of AVI-7288 Drug Product will be shipped to the investigational site pharmacy with cold packs in a validated shipper. Vials must be stored at a consistent temperature from 2 °C to 8 °C in a secured, limited-access area with temperature recording, controls, and monitoring. Placebo (NSS) will be maintained per the manufacturer's specifications.

5.1.5 Preparation and Administration of the Investigational Product

AVI-7288 solution for dosing and placebo (NSS) will be prepared by qualified study staff who do not otherwise participate in collection of study data or have direct contact with participating subjects. Blinded, qualified study staff will administer study drug as an IV infusion over 30 minutes using an infusion pump; study drug will be administered at approximately the same time each day for 14 days.

5.1.5.1 AVI-7288

The dose of AVI-7288 for each dose cohort is noted in Table 5-1 below. The dose of AVI-7288 will be calculated based on the subject's dose cohort and weight, and the appropriate volume of AVI-7288 Drug Product will be drawn into a syringe. The same volume will then be removed from a 150-mL bag of NSS and the syringe of AVI-7288 Drug Product will be injected into the bag of NSS. The bag will then be labeled with the subject's randomization number, and date and time of study drug preparation.

Table 5-1: Study Drug Dosing Regimen by Cohort

Cohort	Dosing Regimen
1	AVI-7288 at 1 mg/kg (or placebo) IV q day x 14 days
2	AVI-7288 at 4 mg/kg (or placebo) IV q day x 14 days
3	AVI-7288 at 8 mg/kg (or placebo) IV q day x 14 days
4	AVI-7288 at 12 mg/kg (or placebo) IV q day x 14 days
5	AVI-7288 at 16 mg/kg (or placebo) IV q day x 14 days

5.1.5.2 Placebo

Placebo control consists of approximately 150-mL NSS; the IV bag will be labeled with the subject's randomization number, and the date and time of preparation.

5.2 Dosing Considerations

5.2.1 Dose Selection Rationale

The present study will examine the safety, tolerability, and PK of 14 once daily IV infusions of 1, 4, 8, 12 or 16 mg/kg AVI-7288, administered in sequential dose cohorts. Pharmacokinetic findings from this study will be compared to the PK of AVI-7288 when administered to nonhuman primates infected with Marburg virus to guide the selection of a human dose for inclusion in the pivotal nonclinical efficacy studies and clinical safety study, as well as the proposed product label.

This trial is the first in man study of AVI-7288 alone; however, AVI-7288 was previously administered to human volunteers in combination with AVI-7287 in the ascending single-dose study of AVI-6003, 6003-us-101. In that study, single IV infusions of AVI-6003 (which is a 1:1 combination of AVI-7287 and AVI-7288) were safe and well tolerated at doses ranging from 0.01 to 9.0 mg/kg, and no clinically significant changes in any of the plasma or urinary kidney biomarkers were observed. At a minimum, these findings suggest that AVI-7288 alone will be safe and well tolerated in humans at doses up to 4.5 mg/kg. The average AUC_{0-24} for the plasma concentrations of AVI-7288 in study 6003-us-101 were ~23,000 ng*hr/mL for the 3 mg/kg dose of AVI-7288 and ~32,000 ng*hr/mL for the 4.5 mg/kg dose of AVI-7288.

Nonclinical studies of AVI-6003 further support the safety of AVI-7288 for human use; 28 daily doses of AVI-6003 were tolerated in nonhuman primates at doses up to and including 200 mg/kg/day and in rats at doses up to 400 mg/kg. Recently, Sarepta Therapeutics conducted a rat study in which the potential reversibility of kidney findings observed in prior animal studies of AVI-6003 (tubular degeneration/necrosis) was investigated. Rats given 1.5, 3, 15, or 30 mg/kg AVI-6003 once a day for 15 days were necropsied at 16 days or 1, 3 or 6 months post last dose. While degeneration in the proximal tubules of the kidney was seen at doses of 15 or 30 mg/kg immediately following dosing (i.e., on Day 16), all such findings were absent by the 1-month recovery period, and all histological findings in the kidney were absent by 6 months post last dose. Based on these findings, the no-observed-adverse-effect level (NOAEL) during the recovery phase was considered to be the highest dose tested of 30 mg/kg/day AVI-6003. At that

dose of AVI-6003, the average exposure to the AVI-7288 component of AVI-6003 after 1 dose was approximately 20,000 ng*hr/mL. Together, the preclinical and human safety data suggest that once daily dosing in humans with 1 mg/kg will be well tolerated and is therefore a justifiable starting dose for this 14-day human study.

As previously mentioned in Section 1, administration of AVI-7288 (alone or in combination with AVI-7287 as part of AVI-6003) once a day for up to 15 days markedly increased the survival of cynomolgus macaques that had been exposed to lethal viral inoculums of Marburg virus, and the efficacy of AVI-7288 appeared dose dependent. Survival rates in animals treated with 3.75 or 7.5 mg/kg of AVI-7288 (as part of 7.5- or 15-mg/kg doses of AVI-6003) were 60%, whereas animals treated with 15.0 mg/kg AVI-7288 (alone or as part of a 30.0-mg/kg dose of AVI-6003) had a survival rate of 92%.

As AVI-7288 was most effective in cynomolgus monkeys at the 15 mg/kg dose, the exposure achieved at this dose level as established in the PK/pharmacodynamic study was compared to the exposures achieved in the human ascending single-dose study, 6003-us-101. Following a dose of 15 mg/kg on day 0, the mean AUC of all infected animals was approximately 78,000 ng*hr/mL, and the mean AUC of all animals (infected and uninfected) was approximately 73,500 ng*hr/mL. The dose expected to provide equivalent exposure in humans is approximately 12 mg/kg, based on linear extrapolation. Therefore, the proposed dose escalation scheme for this human study includes 12 mg/kg. To further define the maximum tolerated dose of AVI-7288 in humans, the proposed highest dose for this human study is 16 mg/kg.

Please refer to the Investigator's Brochure for additional information on the clinical and nonclinical studies referred to in this section.

5.2.2 Dose Escalation

The doses selected for the current human study are 1, 4, 8, 12, and 16 mg/kg, which would encompass a justifiable starting dose (1 mg/kg), an expected efficacious exposure (12 mg/kg) and a higher dose to further define the maximum tolerated dose as outlined above.

An independent DSMB will evaluate the safety of all treated subjects in an ongoing fashion. In addition, the DSMB will convene to review each cohort's cumulative safety data through Day 21 at least once after each cohort has completed dosing in order to make recommendations to the Sponsor concerning the advisability of escalating to the next dose. Additional details regarding the DSMB are included in Section 10.3.

5.2.3 Treatment Interruption or Discontinuation

A subject's study treatment may be discontinued at any time at the subject's request or at the discretion of the Investigator or Sponsor. The following may be justifiable reasons for the Investigator or Sponsor to discontinue a subject from treatment:

- The subject was erroneously included in the study (i.e., was found to not have met the eligibility criteria)

- The subject experiences an intolerable AE
- The subject is unable to comply with the requirements of the protocol
- The subject participates in another investigational study without the prior written authorization of the Sponsor

In addition, dosing of an individual subject will be suspended and the Sponsor will be notified within 24 hours if the subject develops any of the following:

- An SAE, a Grade 4 AE or a Grade 4 laboratory event, for which no clear alternative explanation, other than study drug, exists (Grades are according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" as noted in Section 7.2.2)
- A Grade ≥ 3 rash and/or Grade ≥ 3 allergic reaction (e.g., generalized urticaria, angioedema)
- A Grade ≥ 3 local infusion site reaction, including pain, tenderness, erythema or swelling
- A serum creatinine ≥ Grade 2 toxicity (≥ 1.8 mg/dL)
- A confirmed ≥ 1.5-fold increase in serum creatinine level from baseline
- A confirmed decrease in GFR to < 70 mL/min, irrespective if serum creatinine is normal range or Grade 1
- A confirmed > 3-fold increase from pre-dose on Day 1 in UACR to an absolute value > 30 mg/g

As noted in Section 3.2.1.2, subjects who receive at least 1 dose of investigational product and who are withdrawn from treatment during the dosing period (Days 1 through 14) will be encouraged to remain in the study unit for 48 hours after the last dose of study drug to collect the discharge evaluations (same as Day 16 evaluations) and to return for the Day 21 and Day 42 outpatient visits. Subjects who are withdrawn from the study after the 14-day dosing period will be asked to complete all early termination assessments (same as Day 42 assessments) as soon as possible and the importance of continuing safety follow-up through Day 42 should be stressed.

5.2.3.1 Cohort Stopping Rules

The safety of this study will be overseen by an independent DSMB as noted above and outlined in Section 10.3. If safety concerns arise during the course of the planned DSMB reviews, or outside these reviews, dosing may stop until these concerns have been addressed.
In addition, dosing will be interrupted to allow for an ad hoc review of cumulative safety data by the DSMB if any of the following conditions are met within a cohort:

- Two or more subjects develop the same or clinically similar Grade ≥ 3 AE or laboratory abnormality
- Two or more subjects develop a serum creatinine ≥ Grade 2 toxicity (≥ 1.8 mg/dL)
- Two or more subjects develop ≥ 1.5-fold increase in serum creatinine level from baseline
- Two or more subjects develop GFR < 70 mL/min, irrespective if serum creatinine is normal range or Grade 1
- Two or more subjects who are not menstruating females develop a confirmed > 3-fold increase from pre-dose on Day 1 in UACR to an absolute value > 30 mg/g

The DSMB will be notified by the Sponsor within 24 hours of the Sponsor learning of the events above. The DSMB will evaluate available safety data and may make one of the following recommendations:

- Resume dosing of the subject(s) or dose cohort at the same dose level, a reduced dose level, or the next dose level
- Permanently discontinue dosing of the subject(s) or dose cohort
- Permanently discontinue the study

Any decision to interrupt, restart, or discontinue the study will be made by the Sponsor in consultation with the DSMB. The outcome will be communicated to the Investigator by the Sponsor. The Food and Drug Administration (FDA) will be promptly notified of study suspension or discontinuation related to safety concerns. Any suspension or discontinuation of the trial for any reason will also be promptly reported to the IRB and the US Army Medical Department Medical Research and Material Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO).

5.2.3.2 Determination of the Maximum Tolerated Dose

The maximum tolerated dose (MTD) of AVI-7288 will be the dose below the level at which ≥ 2/6 of subjects on active drug in any specific dose cohort experience any of the following:

- Serum creatinine ≥ Grade 2 toxicity (≥ 1.8 mg/dL)
- Treatment-related AE that is rated as severe

If ≥ 3/6 actively treated subjects in a cohort experience the same treatment-related clinically significant AE, then the MTD is considered exceeded and the next cohort may receive the same or a lower dose as judged appropriate by the DSMB in consultation with the Sponsor and the Principal Investigator.

The MTD may be confirmed by enrolling the next cohort at the same dose. If no additional similar study drug-related AEs are observed, then this dose will be considered the MTD.

In order to make these assessments, the blind for the concerned subjects will be broken. Should any concerned subject be receiving placebo, the DSMB, in conjunction with the Sponsor, may decide to continue the dose escalation as scheduled. This decision may be taken after review of all available safety and tolerability data.

5.3 Prior and Concomitant Medications and Therapeutic Procedures

As specified in the exclusion criteria (Section 4.1) the use of following prior medications are prohibited:

- Nicotine patches, nicotine lozenges, or nicotine gum within 6 months prior to Day -1
- Any other medications (apart from vitamins, acetaminophen, or hormonal contraception) within 14 days prior to the administration of study drug on Day 1 (note that subjects with mild seasonal allergies may have used antihistamines at the discretion of the Investigator after approval by the Sponsor Medical Monitor)
- Any other investigational drug within 45 days prior to the study

The use of alcohol and caffeine is prohibited during the confinement period, i.e. from Day -1 (also referred to as check-in Day) through Day 16

The following concomitant medications may be used during the study, including during the confinement period:

- Vitamins
- Acetaminophen
- Hormonal contraception
- Antihistamines

Other concomitant medications may be used only after receiving prior approval from the Sponsor's Medical Monitor. In addition, medications may be used for the treatment of AEs as needed, using a minimalist approach.

5.4 Method of Assigning Subjects to Treatment

Approximately 130 subjects will be screened to allow a maximum of 40 subjects to be dosed with AVI-7288 or placebo (4 dose cohorts, 8 subjects per cohort).

Qualifying subjects will be randomized sequentially in successive cohorts, with each cohort identified by the first digit of the randomly assigned randomization number (e.g., 101 to 108 will denote subjects in the first cohort, 201 to 208 will denote subjects in the second cohort, and so

on). A subject who has been enrolled and meets all of the inclusion criteria and none of the exclusion criteria at Screening and after evaluation on Day -1 will be randomized within the current cohort through the allocation of the next sequential randomization number on Day 1.

To facilitate enrollment of each cohort, additional subjects may undergo Day -1 assessments simultaneously with those subject(s) designated for dosing on Day 1. These spare subjects will not be randomized unless another subject is disqualified from dosing based on the results of their Day -1 assessments or withdraws from the study after randomization but before initiating dosing. If a spare subject is randomized in place of a subject who is disqualified from dosing based on the results of their Day -1 assessments, then the spare subject should be randomized as described above. If a spare subject is a replacement for a subject who was randomized but did not initiate dosing, the replacement subject will be assigned a randomization number by adding 10 to the randomization number of the subject they are replacing (e.g., the replacement subject is assigned randomization number 111 when replacing the subject who was assigned randomization number 101). The replacement subject will receive the same treatment that was assigned to the subject they are replacing. Spare subjects who are not dosed on a given day may remain in the unit overnight and not undergo any additional procedures, in anticipation of repeating Day -1 evaluations the following day for inclusion in the cohort. Once 8 subjects in a given cohort have initiated dosing, no further subjects will be dosed in that cohort. If a spare subject(s) is not needed for replacement, the subject will have the option to undergo Day -1 assessments with the next dosing cohort (if applicable) and if qualified, the subject will be randomized within that cohort.

Subjects who withdraw from the study after initiating dosing will not be replaced.

5.5 Blinding and Randomization

This is a double-blind study, which means that the subject, the Investigator, study personnel, and Sponsor will be blinded to the treatment assignments (except for as noted below).

The randomization code will be generated by an unblinded statistician at the Contract Research Organization. The study drug will be assigned by an unblinded person who is designated and authorized to dispense study drug according to the randomization code. A second individual who is authorized to verify the dose and assignment will also be unblinded to the subject's treatment assignment. Neither of these individuals will have interaction with the subjects, and both will be instructed not to divulge the randomization assignment to others under any circumstances, unless directed to do so by the Investigator in the interests of the subject's safety.

The blinding code of the study drug must be broken only in exceptional circumstances, such as when knowledge of the study drug is essential for treating a subject due to an SAE. If time permits, the site must contact the Sponsor Medical Monitor, who will in turn authorize the unblinding for that subject. If time does not permit, the Investigator may authorize breaking of the blind and then notify the Sponsor Medical Monitor. If a subject's study treatment is revealed, the subject number, time, date, and reason for unblinding must be recorded in the eCRF; the results of the unblinding should not be recorded in the medical record. Study personnel who were unblinded will also be identified.

5.6 Treatment Compliance

Treatment compliance will be assessed via compliance with daily infusions and will be assured by the staff who administer study drug.

6 EFFICACY AND SAFETY ASSESSMENTS

6.1 Study Schedule of Events

A schedule outlining the study assessments and times of assessments is shown in Appendix I: Schedule of Study Events. Written informed consent to participate in this study must be obtained from the subject prior to participation in any study related assessments or procedures.

6.2 Study Visits

This study will consist of a screening period of up to 21 days (including 1 day to check in to the study unit), a 14-day treatment period, and a 28-day post last dose safety follow-up period. Eligible subjects will check-in to the clinic on Day -1 and complete additional evaluations to confirm eligibility. Eligible subjects will receive once-daily infusions of blinded study drug, AVI-7288 or placebo, on Days 1 through 14, and will be discharged 48 hours after their last dose, on Day 16, provided all assessments are completed and the subject is evaluated as being stable and in good health. Subjects will return to the clinic on Days 21 and 42 to complete safety follow-up.

6.3 Screening Assessments

The screening assessments specified in Appendix I: Schedule of Study Events will be performed in the following order:

- Sign written Informed Consent
- Demographics
- Measurement of height and weight
- Complete medical history (including past blood donation history, tobacco use, and history of previous investigational drug/device study participation)
- Prior and concomitant medications (see Sections 5.3 and 6.4.2.2)
- Urine collection for pregnancy test (in women of childbearing potential), urinalysis, and urinary parameters (see Section 6.4.2.6)
- 12-lead ECG (see Section 6.4.2.3)
- Vital sign measurements (see Section 6.4.2.4)
- Complete physical examination (Section 6.4.2.5)
- Drug screen (screen for use of alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and nicotine. Urine and/or blood testing may be

performed according to the means available to the Phase 1 unit; if urine is used samples will be obtained prior to ECGs)

- Blood collection for pregnancy testing in females of childbearing potential or follicle stimulating hormone (FSH) testing in females to confirm post-menopausal status (as applicable), drug and alcohol screen, chemistry, hematology, coagulation, serology (e.g., HBsAg, HCV, and HIV), and cystatin C (see Section 6.4.2.6)

Note that if abnormal results on screening assessments are obtained that disqualify a subject from participation, such as a positive HIV, HBsAg, or HCV test or any clinically significant (CS) chemistry or hematology result, the subject will be given a copy of the laboratory results and advised to take them to his/her health care provider. If a subject withdraws during the screening period and any significant abnormalities are discovered, every attempt will be made to notify the subject of this fact and encourage the subject to seek appropriate care from his/her primary physician or other health care provider.

6.4 Treatment Period Assessments

6.4.1 Efficacy Assessments

Efficacy data will not be collected during this Phase 1 study.

6.4.2 Safety Assessments

Safety parameters will include the use of concomitant medications, physical examinations, ECGs, vital signs, clinical laboratory testing (e.g., hematology, chemistry, coagulation, urinalysis, and urinary biomarkers), and collection of AEs (from first dose as described in Section 7). Of note, throughout the study, the following assessments will be initiated prior to dosing (unless otherwise specified) and will be performed in the following order:

- Urine collection for safety laboratory assessments, including biomarkers and pregnancy testing in females of childbearing potential
- 12-lead ECG (after the subject has been lying still for at least 15 minutes)
- Vital sign measurements (to be obtained immediately after ECG recording)
- Physical examination
- Blood collection for safety laboratory assessments
- Blood collection for PK testing (immediately before study treatment administration when applicable; see Section 6.5)

It is necessary to maintain the order of assessments as listed above when more than one assessment is requested at any given time point. When multiple assessments are collected, the PK collection should always be taken as close to the exact time noted as possible, and all other

assessments will be collected or performed around that time. The assessment timing should be approximate, but within reason, in relation to the protocol specified time point.

6.4.2.1 Brief Medical History

A brief medical history will be performed at check-in and immediately prior to dosing on Day 1 to capture safety findings that occur prior to subject dosing.

6.4.2.2 Prior and Concomitant Medications and Therapies

Review of all concomitant medications, changes in dosage of concomitant medications, and concomitant therapies will be assessed at each visit from the time the subject has provided signed informed consent.

6.4.2.3 Electrocardiogram

A 12-lead ECG will be obtained at the time points specified in Appendix I: Schedule of Study Events. ECGs will be performed only after the subject is positioned supine, resting, and quiet for a minimum of 15 minutes.

ECGs will be performed in triplicate (with at least 1 minute between each ECG) during Screening, on Day -1 and prior to dosing on Day 1; all other scheduled ECGs will be performed a single time.

On dosing days, post-dose ECGs will be performed approximately 1 hour after completion of dosing.

ECGs will be sent to a central ECG laboratory and reviewed and interpreted by a cardiologist. The interpretation of the report will be documented and sent to the site. The Investigator will receive and review the results of the ECG report and designate the abnormal findings as CS or not clinically significant (NCS).

6.4.2.4 Vital Signs

Vital signs (oral temperature, pulse, respiratory rate, and blood pressure) will be measured after subjects have remained at rest for a minimum of 5 minutes at the time points specified in Appendix I: Schedule of Study Events. Pulse and respiratory rate will be measured over 1 minute; oral temperature will be recorded in degrees Celsius (° C).

Vital signs will be measured prior to dosing and approximately 1 hour after initiation of dosing on all dosing days, as well as 24 and 48 hours after the last dose of study medication is administered.

In addition, blood pressure will also be measured 10 and 30 minutes after the first and second doses of study drug are initiated; continued measurement of blood pressure at 10 and 30 minutes after initiation of dosing on subsequent dosing days is at the discretion of the Investigator.

Clinically significant changes from just prior to dosing will be documented in the subject source records and eCRF as an AE.

6.4.2.5 Physical Examination

Complete physical examinations will be conducted at the time points specified in Appendix I: Schedule of Study Events. Physical examinations will be performed by the Investigator, an MD Sub-Investigator, a Physician's Assistant, or a Nurse Practitioner (if licensed in the state to perform physical examinations), and will include assessment of general appearance; skin; lymph nodes; head, eyes, ears, nose, and throat (HEENT); chest/lungs; abdomen, and the cardiovascular, musculoskeletal, and neurological systems. Clinically significant changes from just prior to first dose will be documented in the subject source records and eCRF as an AE.

In addition, focused physical examinations may be performed throughout the study on an as-needed basis, e.g., when assessing symptoms of an AE.

6.4.2.6 Clinical Laboratory Tests

The following clinical laboratory tests will be collected at the time points specified in Appendix I: Schedule of Study Events and analyzed by an accredited laboratory selected by the Sponsor (see Appendix V: Additional Study Information):

Urinalysis[a]:	Bilirubin, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, microscopy, urine microscopy including red blood cells (RBC), white blood cells (WBC), bacteria, yeast, epithelial cells and other abnormalities such as casts, crystals and renal tubular epithelial cells
Urinary parameters[a]:	Quantitative albumin, total protein, creatinine
Urinary biomarkers[a]:	Kidney injury molecule-1 (KIM-1), cystatin C, and β2-microglobulin, each normalized to urine creatinine
Hematology:	RBC, WBC, hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and abnormal cells (if applicable)
Coagulation:	Prothrombin time (PT), activated partial thromboplastin time (aPTT)
Full chemistry[b]:	Sodium, chloride, potassium, calcium, glucose, creatinine, blood urea nitrogen (BUN), albumin, uric acid, total bilirubin, alkaline phosphatase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total protein, and cholesterol
Limited chemistry:	BUN and creatinine

Additional parameters:	Serum cystatin C
Pregnancy testing:	Urine and serum pregnancy testing

[a]Use first morning urine on days when subject is confined to the unit.
[b]GFR will also be calculated based on the MDRD equation at the indicated timepoints.

Any value outside of the current reference ranges for the laboratory performing the test will be flagged on the laboratory results. The Investigator will score all abnormal assessment results as either CS or NCS. Clinical significance (CS) is defined as any variation in assessment results that has medical relevance resulting in an alteration in medical care. If clinically significant deterioration from baseline levels is noted, the changes will be documented in the eCRF as an AE, according to Section 7.4. The Investigator will continue to monitor the subject with additional assessments until:

- Values have reached normal range and/or baseline levels; or
- In the judgment of the Investigator together with the Sponsor Medical Monitor, abnormal values are not related to the administration of test article or other protocol-specific procedures, and additional assessments are not medically indicated

6.5 Pharmacokinetic Assessments

Blood and urine samples for PK analysis will be collected at the time points specified in Appendix I: Schedule of Study Events and indicated below:

On Day 1:

- Plasma for PK sampling will be collected immediately pre-dose, at approximately 10 and 30 minutes after completion of dosing, and at approximately 1, 1.5, 2, 4, 6, 8,12, 16, and 24 hours after completion of dosing (collection of plasma 24-hours post dose will also serve as the trough sample for Day 2)
- Urine for PK sampling will be collected during the following time intervals: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after initiation of dosing. Subjects will be asked to void within 30 minutes before dosing to empty bladder pre-dose, and then at approximately 4, 8, 12 and 24 hours after initiation of dosing to complete the preceding urine collection interval

On Day 14:

- Plasma for PK sampling will be collected immediately pre-dose, at approximately 10 and 30 minutes after completion of dosing, and at approximately 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 28, 32, 36, and 48 hours after completion of dosing (collection of plasma pre-dose on Day 14 will also serve as the trough sample for that day)

- Urine for PK sampling will be collected during the following time intervals: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after initiation of dosing. Subjects will be asked to void within 30 minutes before dosing to empty bladder pre-dose, and then at approximately 4, 8, 12, and 24 hours after initiation of dosing to complete the preceding urine collection interval

Plasma for PK sampling will also be collected immediately prior to dosing each day for determination of trough values.

7 ADVERSE EVENT REPORTING

Subjects will be evaluated for new AEs and the status of existing AEs on an ongoing basis as indicated in Appendix I: Schedule of Study Events. The Investigator may elicit symptoms using an open-ended question, followed by appropriate questions that clarify the subject's verbatim description of AEs or change in concomitant medications. All AEs from initiation of first dose through Day 42 will be recorded in the subjects' source documentation and then in the eCRF. As noted in Section 7.3.1, AEs occurring after signed informed consent has been obtained and prior to initiation of dosing will be recorded as medical history.

7.1 Definitions

7.1.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject, which does not necessarily have a causal relationship with the investigational product (active or placebo drug, biologic, or device). An AE can therefore be any unfavorable and unintended symptom, sign, disease or condition, or test abnormality whether or not considered related to the investigational product.

Adverse events include:

- Symptoms described by the subject or signs observed by the Investigator or medical staff
- Test abnormalities (laboratory tests, ECG, etc.) that result in an alteration in medical care (diagnostic or therapeutic)

Abnormalities present at baseline are considered AEs only if they reoccur after resolution or they worsen during the study.

7.1.1.1 Unexpected Adverse Events

In this study, an unexpected AE is one which:

- Is not previously reported as associated with AVI-7288 (or AVI-6003), as referenced in the Investigator's Brochure
- May be symptomatically and pathophysiologically related to an AE listed in the Investigator's Brochure, but differs from the event because of greater severity or specificity

FDA-reportable AEs are AEs that are associated with the use of the drug and are serious and unexpected.

7.1.2 Definition of a Serious Adverse Event

An SAE is any AE that results in any of the following:

Death: The subject died as the result of the event.

Life-threatening event: Any AE that places the subject, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that, had it occurred in a more severe form, might have caused death.

Requires or prolongs inpatient hospitalization: The AE resulted in an initial inpatient hospitalization or prolonged an existing hospitalization of the patient/subject. If a patient/subject is hospitalized as part of the clinical use of the product, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.

Persistent or significant disability/incapacity: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.

Congenital anomaly/birth defect: A congenital anomaly/birth defect that occurs in the offspring of a subject exposed to the investigational product.

Important medical events: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.2 Evaluation of Adverse Events/Serious Adverse Events

7.2.1 Relationship to Study Treatment

Assessment of the association between the AE and study exposure is important for regulatory reporting. For each AE/SAE, the Investigator determines whether there is a reasonable possibility that the AE may have been caused by the study treatment according to the categories below:

- **Unrelated:** The event is clearly not related to study drug
- **Possibly Related:** The event could be related to study drug
- **Probably Related:** The event is likely related to study drug
- **Definitely Related:** The event is clearly related to study drug

In judging relationship to investigational product, it is expected that the temporal sequence of onset of the event during or after administration of investigational product and the existence of other potential causes will be taken into account. AEs that the Investigator considers to be possibly, probably, or definitely related to the study drug will be considered to constitute drug-related AEs for the purposes of analysis and regulatory reporting.

A relationship to the investigational product must be given for each AE/SAE recorded, even if there is only limited information at the time. The Investigator may change his/her opinion of causality in light of follow-up information, amending the AE/SAE report accordingly.

7.2.2 Severity Grading of Adverse Event Scoring

Note that severity should not be confused with seriousness, the latter of which is defined in Section 7.1.2, and which serves as a guide for defining regulatory reporting obligations.

The Investigator will determine the severity of an AE using the criteria specified in the FDA's guidance document, "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" (2007). This scale, which will be provided to the Investigator and staff, was selected for this study because it has been developed by the FDA in conjunction with external input, and is specifically designed for assessing AEs in healthy volunteers who receive a prophylactic intervention.

For each AE, the Investigator should record the severity grade attained according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" criteria, where applicable, as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening). If grading criteria do not exist for a specific AE, the Investigator should grade the severity of the AE using the following guidelines:

Grade 1 (Mild):	Awareness of sign or symptom, but easily tolerated; of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation.
Grade 2 (Moderate):	Discomfort or functional impairment sufficient to cause mild interference with usual activities; may require active therapeutic intervention.
Grade 3 (Severe):	Moderate to marked interference with usual activities and/or substantial dysfunction involving one or more organ or body systems; requires therapeutic intervention.
Grade 4 (Life-threatening):	An AE that places the subject's life in immediate jeopardy.
Grade 5 (Fatal):	An AE that is fatal.

7.2.3 Outcome

Outcome describes the status of the AE. The Investigator will provide information regarding the subject outcome of each AE.

7.2.4 Action Taken Regarding the Investigational Product

The Investigator will provide information regarding the action taken with respect to the investigational product in response to the AE.

7.3 Timeframe for Collection of Adverse Events/Serious Adverse Events

7.3.1 Adverse Events Occurring Prior to Study Treatment

Any or AEs or SAEs occurring after informed consent has been obtained and prior to initiation of study drug will be recorded as medical history.

7.3.2 Adverse Events Occurring During and After Study Treatment

Adverse events and SAEs will be collected from initiation of study drug on Day 1 through Day 42 or early termination.

AEs will be collected on an ongoing basis. In addition, on dosing days (Days 1 through 14) the subject should be assessed for AEs immediately prior to and approximately 1 hour after dosing.

7.3.3 Adverse Events Occurring Following Subject Discontinuation of Treatment

For subjects who have received at least 1 dose of study drug and who prematurely discontinue study treatment or the study, AEs will continue to be recorded until at least 30 days after the last dose of study drug where possible. See Section 7.3.4 for reporting requirements after the subject completes the study.

7.3.4 Serious Adverse Events Occurring Following Subject Completion of the Study

If, at any time after the subject has completed participation in the study (as defined in Section 3.2.1.1), the Investigator or study personnel becomes aware of an SAE that the Investigator believes is possibly, probably, or definitely related to the investigational product (see Section 7.2.1), then the event and any known details should be reported promptly to the Sponsor. Reporting of SAEs will be done according to the instructions in Section 7.5.

7.4 Recording of Adverse Events/Serious Adverse Events

All AEs/SAEs experienced by the subject will be recorded in the subject's source documentation and then in the eCRF. Information including a concise description of the event; date and time of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to investigational product; and action taken regarding the investigational product will be recorded. Resolution occurs when the subject has returned to his/her baseline state of health or further improvement or worsening of the event is not expected.

Abnormalities in vital signs, laboratory results, and other safety assessments noted in Section 6.4.2 will be recorded as an AE if they meet the definition of an AE (see Section 7.1.1).

When possible, a diagnosis should be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to that diagnosis. A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. If the condition is not known, the procedure must be reported as an AE instead. Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE.

All SAEs experienced by the subject will be recorded on an SAE Report Form and reported to the Sponsor according to Section 7.5.

7.5 Reporting of Serious Adverse Events

The necessity and time requirements for reporting of SAEs to the Sponsor or its designee and/or regulatory agencies are as follows:

- All SAEs must be reported to the Sponsor/designee within 1 calendar day of the Investigator's first knowledge of the event by fax or e-mail regardless of relationship to study procedures or treatment. The Investigator is requested to supply detailed information regarding the event at the time of the initial report.

- A completed Clinical Study SAE Report Form containing a detailed written description of the event along with additional supporting documents (e.g., discharge letters, autopsy reports, and other documents) will be faxed to the Sponsor or Sponsor designee within 2 calendar days of the Investigator's first knowledge of the event. (If faxed within 1 calendar day of the Investigator's first knowledge, this form may serve as the initial notification.)

- Follow-up information, which may include copies of relevant subject records and other documents not available at the time the initial SAE Report Form was completed, must be sent to the Sponsor or Sponsor Designee as soon as available. Follow-up SAE reports may describe the evolution of the reported events and any new assessment of their outcome and/or relationship to treatment. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant subject/hospital records and pathology or autopsy reports.

- Investigators will receive copies of expedited safety reports that the Sponsor sends to regulatory agencies. The Investigator is responsible for fulfilling local reporting requirements to their IRB. Investigators will report events to their IRB in accordance with applicable standard operating procedures and/or local reporting requirements. Investigators must forward copies of the IRB notification to the Sponsor.

7.5.1 Follow Up of Adverse Events/Serious Adverse Events

All AEs/SAEs documented at a previous contact that are designated as not recovered/not resolved or recovering/resolving will be reviewed by the Investigator at subsequent contacts.

The Investigator will provide follow-up information for any SAE to the Sponsor or Sponsor designee as soon as it is available. The Sponsor or regulatory authorities may request additional information regarding an SAE.

All AEs will be followed until the resolution of AE, completion of the subject's participation, or study termination, whichever occurs first. Serious AEs will be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is no longer necessary.

Rules for AE/SAE follow-up apply to all subjects, including those withdrawn prematurely to the extent allowed by the subject's consent. The Investigator will ensure that follow-up includes further investigations consistent with appropriate medical management and subject consent to elucidate the nature and/or causality of the AE/SAE.

7.6 Pregnancy Reporting

If a female subject becomes pregnant at any time after the first dose of study treatment, she must be discontinued from study treatment immediately and followed by the Investigator at least until the outcome of the pregnancy is known (i.e., delivery, elective termination, spontaneous abortion, etc.). If it becomes known that the female partner of a male subject becomes pregnant during the treatment or follow-up period of this study, the pregnancy will be followed until the outcome of the pregnancy is known. During the follow-up period, the Investigator must report on any subsequent treatments and the outcome of the pregnancy to the Sponsor. If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The Investigator must notify the Sponsor (via fax) within 24 hours of first learning of the occurrence of a pregnancy in a female subject or the sexual partner of a male subject, and provide the date of the last menstrual cycle. When the Investigator becomes aware of the pregnancy outcome, this information must also be reported to the Sponsor within 24 hours.

7.7 Additional Study-Specific Safety Reporting Requirements

In addition to the reporting requirements specified above, all unanticipated problems involving risk to subjects or others, SAEs, and all subject deaths associated with the study must be promptly reported to the US Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO) by phone ([301] 619-2165), e-mail (hsrrb@amedd.army.mil), or facsimile ([301] 619-7803).

In addition, the study's Independent Medical Monitor must review all unanticipated problems involving risk to subjects or others, SAEs, and all subject deaths associated with the study and provide an unbiased written report of the event to the USAMRMC ORP HRPO within 10 calendar days. At a minimum, the Medical Monitor should comment on the outcomes of the event or problem and, in the case of an SAE or a death, on the relationship to participation in the study. The Medical Monitor should also indicate whether he/she concurs with the details of the report provided by the Investigator. Reports for events determined by either the Investigator or the Medical Monitor to be possibly, probably, or definitely related to participation and reports of events resulting in death should be promptly forwarded to the HRPO. The Medical Monitor may

not necessarily be on site during all study procedures but will remain in close contact with the Investigator during the conduct of the study and will be available by cell phone around the clock.

Complete reports may be emailed or faxed (e-mail: hsrrb@amedd.army.mil; facsimile: [301] 619-7803) or sent to the following address:

US Army Medical Research and Materiel Command
ATTN: MCMR-RPH
504 Scott Street
Fort Detrick, MD 21702-5012

8 DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

8.1 Recording of Data

The Investigator or personnel designated by the Investigator will perform primary data collection based on source-document or clinic records or other source documentation. All required study information must be recorded on the appropriate eCRF screens/forms. The eCRFs are considered complete when all data fields are completed. The Study Monitor will conduct 100% source data verification to ensure maximum data integrity before review and approval of each subject's eCRF. In addition, as the person ultimately responsible for the accuracy of all eCRF data, the Investigator will provide electronic endorsement that the data on the eCRFs are accurate and complete.

8.2 Data Quality Assurance

The eCRFs will be reviewed by a clinical monitor from the Sponsor or a representative of the Sponsor against the source notes for identification and clarification of any discrepancies. Automated quality assurance programs will be in place to identify discrepancies, such as missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be documented on electronic data clarification requests (eDCRs) and forwarded to the Investigator or study coordinator for resolution. All changes to the eCRFs will be tracked to provide an audit trail.

The Investigator must make study data accessible to the Study Monitor, to other authorized representatives of the Sponsor, and to the appropriate regulatory authority inspectors.

8.3 Data Management

The Sponsor in close collaboration with any designee will be responsible for:

- database creation and validation
- eCRF review and data validation
- query resolution
- data analysis and reporting

8.4 Protocol Deviations

A deviation from the protocol is defined as any unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB and agreed to by the Investigator. Deviations can have an impact on individual subjects or a small group of subjects and can involve inclusion/exclusion or primary endpoint criteria. Deviations also occur when there is non-adherence to the protocol that results in a significant, additional risk to the subject, when the subject or Investigator has failed to adhere to significant protocol requirements and the subject

was enrolled without prior Sponsor notification and IRB approval, or when there is non-adherence to FDA regulations and/or International Conference on Harmonisation (ICH) E6. Deviations from the protocol will be documented and reported to the IRB as required.

9 STATISTICAL METHODS AND PLANNED ANALYSES

9.1 General Considerations

This section describes the plan for the rules and conventions to be used in the analysis and presentation of data for study protocol 7288-us-101.

This plan may be revised during the study to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution that could affect planned analyses. These revisions will be based on blinded review of the data, and a final plan will be issued prior to database lock.

All available data will be included in data listings and tabulations. No imputation of values for missing data will be performed.

Percentages of subjects with AE or laboratory toxicities will be based on non-missing values.

Baseline will be defined as the last available value before dosing, or the mean of the Day -1 and Day1 pre-dose value, as appropriate.

A formal statistical analysis plan for the analysis and presentation of data from this study will be prepared before database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

Placebo-treated subjects will be pooled across all dose groups.

Statistical analysis will be performed by or under supervision of the Sponsor.

9.2 Determination of Sample Size

Sample size for this study was based upon qualitative considerations. No formal sample size calculations were performed.

The following table provides probabilities for observing at least one AE within any particular dose cohort, for various incidence rates and sample sizes.

Table 9-1: Probabilities for Observing Adverse Events

	Incidence Rate		
Sample Size	**0.02**	**0.10**	**0.30**
6	0.11	0.47	0.88
8	0.15	0.57	0.94
10	0.18	0.65	0.97

For example, if a rare event occurs 2% of the time, the probability that at least 1 subject experiences this event is 11% in any cohort with 6 subjects receiving AVI-7288.

Furthermore, the results from study 6003-us-101 showed low inter-subject variability for C_{max} (coefficient of variation [CV] range of 1.5 to 35.7%) and AUC_{0-24} (CV range of 5.1 to 32.7%) with 4 subjects per cohort suggesting the proposed sample size of 6 subjects per cohort receiving AVI-7288 is reasonable for this type of study.

9.3 Analysis Sets

All analyses except PK analyses will be performed using the Safety Set. If incorrect treatment is assigned, subjects will be analyzed according to the treatment they actually received for both analysis data sets.

9.3.1 Safety Set

The Safety Set will include all randomized subjects who receive any amount of study drug.

9.3.2 Pharmacokinetic Set

The Pharmacokinetic Set will include all randomized subjects who receive the full dose of study drug and for whom there are adequate PK samples from which to estimate PK parameters.

9.4 Demographics and Baseline Characteristics

Subject demographic data (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, BMI) will be listed for all subjects and summarized by dose group and for all subjects.

9.5 Subject Accountability

The number and percentage of subjects completing or prematurely discontinuing the study will be summarized by dose group. Reasons for premature discontinuation will be summarized.

9.6 Study Treatment Usage and Compliance

The total number of infusions administered as well as the cumulative exposure to study drug will be summarized by dose group.

9.7 Efficacy Analyses

Not applicable.

9.8 Safety Analyses

All subjects who are randomly assigned to a treatment group within each dose cohort and receive at least 1 dose of the study drug will be included in the safety and tolerability analyses.

Safety evaluations will be based on the incidence, intensity, and type of AE and clinically significant changes in the subject's physical examination findings, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented for all subjects who receive study drug, i.e., the safety set.

Abnormalities in clinical laboratory findings, vital signs, and ECGs will be based on pre-defined normal ranges and will be tabulated by dose group showing subject counts and percentages.

9.8.1 Physical Examination and Vital Signs

Descriptive statistics will be provided to evaluate raw data and change from baseline at each scheduled time point. Normal reference ranges and pre-defined change abnormal results will be used in the summary of vital signs data. Results of physical examinations will be listed.

9.8.2 Clinical Laboratory Tests

Laboratory data will be summarized by the type of laboratory test. Normal reference ranges and pre-defined change abnormal results will be used in the summary of laboratory data. Raw data and change from baseline in clinical laboratory parameters will be summarized using descriptive statistics. Shift tables will be produced for selected laboratory parameters. A listing of subjects with any laboratory results outside the reference ranges will be provided.

Changes in renal function tests will be analyzed to identify trends that may not be readily detectable in an analysis of group mean values over time. Specifically, at each time point, the number and percentage of subjects in each cohort with Grade 1, Grade 2, Grade 3 or Grade 4 toxicity serum creatinine levels will be presented. In addition, the number and percentage of subjects who meet the following criteria will be presented:

- A $\geq$ 1.5-fold increase in serum creatinine level from baseline
- A decrease in GFR to < 70 mL/min
- A > 3-fold increase in UACR from baseline to an absolute value of > 30 mg/g
- A > 30% increase in serum cystatin C from baseline to a level above the normal (reference) range

9.8.3 Adverse Events

The original terms used in the eCRF by Investigators to identify AEs will be coded using the current version of the Medical Dictionary of Regulatory Activities (MedDRA). The percentage of subjects with specific treatment-emergent AEs will be summarized for each treatment.

Special attention will be given to those subjects who have discontinued treatment due to an AE or who experienced a severe or a serious AE.

All AEs will be presented in a subject data listing.

9.8.4 Concomitant Medications

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. These data will be presented in a subject data listing.

9.8.5 Twelve-Lead Electrocardiograms

12-lead ECG variables will be evaluated by means of descriptive statistics for raw and change from baseline data, as well as by frequency tabulations. Normal reference ranges and pre-defined change abnormal results will be used in the summary of all ECG data. All important abnormalities from the ECG readings, including changes in T-wave morphology and/or the occurrence of U-waves versus baseline recordings, will be reported.

9.9 Pharmacokinetic Analysis

The PK analysis at the specified dose levels will be based on blood and urine samples for the AVI-7288-treated subjects.

Data will be listed for all subjects with available plasma concentrations per dose group and treatment. All concentrations below the quantification limit (BQL) or missing data will be labeled as such in the concentration data listings. Concentrations identified as BQL will be treated as 0 in the summary statistics and for the calculation of PK parameters.

Pharmacokinetic parameters for AVI-7288 will be calculated using non-compartmental analysis. Actual sampling times will be used in all final PK parameter estimations. Per-protocol times will be used to calculate mean plasma concentrations for graphical displays and summary tables.

C_{max} and T_{max} will be taken directly from the data. The elimination rate constant, λ_z, will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The range of data to be used for each subject and dose will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time. Other PK parameters will be calculated as described in Section 3.1.3. All PK calculations and figures will use validated software.

Listings of individual subject plasma concentrations, actual blood sampling times, and PK parameters and graphs of concentration vs. time will be prepared by dosing cohort. Plasma concentrations and PK parameters will be summarized by and compared among dosing cohorts using mean, standard deviation (SD), coefficient of variation (CV), and minimum, and maximum.

Dose proportionality for C_{max} and AUC(s) will be assessed visually by plotting these parameters (original and dose-normalized) against dose. Further statistical analyses may be performed to assess dose proportionality. Accumulation ratios for C_{max} and AUC(s) and time to steady state will also be assessed.

The PK profile following 14 daily doses (Day 14 profile) will be graphically compared to that following a single dose (Day 1 profile).

In addition, the following PK parameters will be calculated from the urine levels of AVI-7288:

- Amount excreted for each defined urine collection time point
- Cumulative amount excreted over time (up to 1 day after last administration)
- Cumulative percentage of injected AVI-7288 excreted in the urine
- Calculated Cl_R (i.e., urinary clearance)

For each subject, renal clearance will be estimated as total amount of AVI-7288 that is excreted during a 24-hour sample collection period divided by AUC_{0-24}.

9.10 Interim Analyses

Interim analyses of safety will be performed on a per-cohort basis and evaluated by the DSMB. The content of these analyses will be specified in the DSMB charter, which will be ratified by the independent members of the DSMB.

9.11 Other Statistical Issues

Additional analyses may be conducted. Any such analyses will be detailed in the Statistical Analysis Plan.

10 SPECIAL REQUIREMENTS AND PROCEDURES

10.1 Compliance with Ethical and Regulatory Guidelines

This study was designed and will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in conformance with ICH Good Clinical Practice (GCP) E6 guidance documents. The study will comply with the requirements that are enunciated in the US Code of Federal Regulations (CFR) related to the protection of human subjects (21 CFR Part 50), IRBs (21 CFR Part 56), INDs (21 CFR Part 312), electronic records and electronic signatures (21 CFR Part 11), and financial disclosure (21 CFR Part 54).

10.2 Institutional and Ethics Review

This study will be conducted in full compliance with the IRB regulations in 21 CFR 56. Before enrollment of subjects into the study, the protocol and informed consent documents will be reviewed and approved by an IRB that is in compliance with 21 CFR 56. Amendments to the protocol will be subjected to the same IRB review requirements as the original protocol. The Investigator will promptly notify the IRB and Sponsor of any serious or unexpected AEs or of any other information that might affect the safe use of the study drug during the study. A letter documenting the IRB approvals must be sent to the Sponsor before initiation of the study or before an amendment is instituted. All correspondence with the IRB should be retained in the study files.

10.3 Data Safety Monitoring Board

An independent DSMB will be assembled by the Sponsor and will consist of up to 5 members with relevant experience and expertise (including at least 1 with expertise in nephrology). The Sponsor will facilitate drafting and ratification of a DSMB charter; however, the content of the charter, including the specific safety monitoring that falls within the purview of the DSMB and the DSMB structure, frequency of meetings, remittance, procedures, and administrative support, must be approved by the members of the DSMB. The DSMB will evaluate the study experience and outcome of all treated subjects in an ongoing fashion, focusing on subject safety, and will convene at least once after each cohort, prior to escalation to the next dose level. The DSMB may convene more frequently if required based upon the safety experience of individual subjects.

Blinded study data will be provided to the DSMB but, if necessary, in light of an AE or pattern of AEs, the DSMB may ask for the blind to be broken to allow the members to ascertain whether continuation of the trial is acceptable and warranted. The DSMB will be responsible for providing recommendations to the Sponsor concerning the advisability of dose escalation and continuation of the trial in the setting of a possible safety signal.

10.4 Informed Consent and Authorization for Use and Disclosure of Protected Health Information

Written informed consent and written authorization of use and disclosure of protected health information (PHI) from each subject must be obtained before any study-specific screening or

baseline period evaluations are performed. One copy of the signed informed consent document and the signed authorization for use and disclosure of PHI will be given to the subject; the Investigator will retain the original copies of these documents.

The informed consent document and authorization for use and disclosure of PHI, which are prepared by the Investigator or the site, must be reviewed and approved by the Sponsor, and the IRB before initiation of the study. The informed consent document must contain the basic required elements of consent and additional elements, as applicable, as specified in 21 CFR 50.25. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508(b) in the US for valid authorizations.

10.5 Confidentiality

10.5.1 Data

All information regarding the nature of the proposed investigation that is provided to the Investigator by the Sponsor, the Sponsor's designee, or the Study Monitor, with the exception of information that is required by law or regulations to be disclosed to the IRB or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current Health Insurance Portability and Accountability Act (HIPAA) standards.

10.5.2 Subject Anonymity

The anonymity of participating subjects will be maintained to the extent required by applicable laws and in accordance with current HIPAA standards. Subjects will be identified by their initials and an assigned subject identification number on the eCRFs and other documents that are reviewed by the Study Monitor. The Investigator must maintain all documents related to the study that identify the subject (e.g., the signed informed consent document) in strict confidence, except to the extent necessary to allow auditing by the appropriate regulatory authorities, the IRB, the Study Monitor, or the Sponsor or its representatives.

10.6 Changes to the Conduct of the Study or Protocol

Changes to the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, doses, assessment variables, the number of subjects to be treated, or the subject selection criteria. Such changes must be documented as a protocol amendment by the Sponsor and must only be implemented upon joint approval of the Sponsor, Investigator, and IRB.

A protocol amendment must receive IRB approval before implementation. In parallel with the IRB-approval process, the protocol amendment will be submitted to the FDA as an amendment to the IND application. If a protocol amendment requires changes in the informed consent document, the revised document must be reviewed and approved by the Sponsor before review and approval by the IRB.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed by the Investigator as crucial for the safety and well-being

of that subject may be instituted for that subject only. The Investigator will contact the Sponsor Medical Monitor as soon as possible regarding such a departure. These departures do not require preapproval by the IRB; however, the IRB and Sponsor Medical Monitor must be notified in writing as soon as possible in accordance with the IRB policies after the departure has been made; the HRPO must also be notified of any deviation to the protocol that may have an effect on the safety or rights of the volunteer or the integrity of the study. In addition, the Investigator will document the reasons for the protocol deviation and the ensuing events in the subject's eCRF. Documentation of IRB approval of any amendments must be returned to the Sponsor or designee.

10.7 Additional Study-Specific Requirements

Additional study requirements as specified in the "Guidelines for Investigators: Requirements for U.S. Army Medical Research and Materiel Command (USAMRMC) Headquarters Level Administrative Review and Approval of Research Involving Human Volunteers, Human Anatomical Substances, and/or Human Data" guidance document (dated 30 August 2010) not already addressed in the body of this protocol are included in Appendix V: Additional Study Information.

11 STUDY DOCUMENTATION AND ADMINISTRATIVE DATA

11.1 Case Report Forms

An eCRF is required and must be completed for each subject, with all required study data accurately recorded such that the information matches the data contained in medical records (e.g., physician's notes, clinic charts, and other study-specific source documents). The Investigator or designee (e.g., study coordinator) will be trained in the use of the study-specific eCRFs and will enter the data for each subject directly into the eCRFs.

Source documents will be filled out legibly and completely in ink. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the source documents will be crossed out with a single line, initialed and dated, and the correct entry, if appropriate, will be recorded. The original source documents will be provided to the Sponsor or designee. These source documents will be maintained in the Investigator's site file. Illegible or incomplete entries or entries needing additional explanation will be queried to the Investigator for clarification.

Data will be entered by the site onto the eCRFs. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the eCRFs should be corrected. Changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail, and should include the reason for change. Incomplete entries or entries needing additional explanation will be highlighted or queried to the Investigator for clarification.

The eCRFs will be reviewed and source verified by the Study Monitor (e.g., clinical research associate) during periodic site visits. During the data collection process, automated quality assurance programs will be in place to identify discrepancies, such as missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be documented on eDCRs and forwarded to the Investigator or study coordinator for resolution. The Investigator or study coordinator will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate. All changes to the eCRFs will be tracked to provide an audit trail. The Investigator has the final responsibility for the accuracy of all clinical data that are entered on the eCRFs and will be required to provide written endorsement that the data are accurate and complete via electronic signature.

11.2 Study Files

Documentation concerning Investigator data (e.g., a signed Form FDA 1572, curriculum vitae, and completed and signed Financial Disclosure Form), IRB data (including documentation of IRB approval and compliance), and clinical laboratory information, as well as the signed protocol page and a blank copy of the IRB-approved informed consent document and authorization, are among the critical documents required before study site initiation visit is to occur (see Appendix II: Requisite Documents for Approval of Study Site). Copies of these documents, as well as supplemental information, such as the Investigator's Brochure, responsibilities and obligations of Investigators and Sponsor, final protocol, and a detailed description of the Sponsor and Investigator responsibilities (see Appendix III: Responsibilities

of Sponsors and Investigators) must be kept onsite in a special study file. This file also will contain a copy of the blank eCRFs (i.e., copies of blank data entry screens), subject accountability records, drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB correspondence, amendments to the protocol, information on monitoring activities, biological sample records, and SAE and safety reports.

11.3 Study Monitoring and Data Quality Control and Quality Assurance

Study monitors who have been selected and prequalified by the Sponsor for their experience, education and training, in accordance with the Sponsor's requirements and after having documentation of training in the applicable FDA regulations, ICH guidelines and GCP, and study-specific procedures and protocol, will ensure that the study is conducted and documented properly by carrying out the relevant activities, as outlined in GCPs (ICH E6, Section 5.18.4). The progress of the study will be monitored through:

- Periodic on-site visits
- Frequent telephone communications between the site (Investigator and study coordinator) and the Study Monitor(s), Sponsor Medical Monitor and Sarepta Therapeutics
- Review of eCRFs, source documentation, and clinical records
- Following the approved monitoring plan

Sponsor representatives may accompany the Study Monitor to the site during scheduled visits.

Audits may be carried out by the Sponsor's representatives, and inspections may be performed by regulatory authorities or IRBs before, during, or after the study. The Investigator will allow and assist the Sponsor's representatives and any regulatory agency to have direct access to all study records, eCRFs, subject medical records, and other source documentation, investigational product dispensing records and investigational product storage area, study facilities, and any other documents considered source documentation. Audit certificate(s) will be provided.

Representatives of the USAMRMC are also eligible to review research records.

11.4 Retention of Study Documents

The supporting documentation and administrative records all must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. Furthermore, in compliance with ICH E6, essential documents should be retained until 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 investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No

study documents will be destroyed or moved to a new location without prior written notification to and approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records that are required to be maintained for the study should be transferred to an agreed-upon designee.

Subject records or other source data must be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If offsite archiving is used, all records should be retrieved and made available for review at the time of an audit or regulatory authority inspection.

11.5 Termination of Study or Study Site

If the Sponsor, the Investigator, the Sponsor Medical Monitor, the Study Monitor, IRB, or appropriate regulatory officials discover conditions arising during the study that indicate the study should be halted or that the study center should be terminated, appropriate action may be taken after consultation among the Sponsor, the Investigator, IRB and the Sponsor Medical Monitor.

Conditions that may warrant termination of the study or an individual site include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of the IRB or appropriate regulatory authorities such as the statement of the Investigator (Form FDA 1572), or 21 CFR Part 11, 50, 54, or 312
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, IRB, or regulatory authority
- Insufficient adherence to protocol requirements consistent with 21 CFR 312.60, or insufficient compliance with the signed agreement (Form FDA 1572), the general investigational plan (protocol), or the requirements of 21 CFR 312

Study termination and follow-up will be performed in compliance with the conditions set forth in the ICH E6 guideline on GCP (Sections 4.12, 4.13, 5.20, and 5.21) as well as 21 CFR 312.56(b), which requires a Sponsor to ensure an Investigator's compliance with the signed agreement (Form FDA 1572), the general investigational plan (protocol), or the requirements of 21 CFR 312 or other applicable parts and to promptly either secure compliance or discontinue

shipments of the investigational new drug to the Investigator and end the Investigator's participation in the investigation.

11.6 General Information

The Investigator should refer to the associated most current and up-to-date Investigator's Brochure, the information that is provided during the study initiation visit, the information that is provided by the Study Monitor during routine monitoring visits, and the appendices of this protocol for further information on this investigational new product or details of the procedures that are to be followed during this study.

11.7 Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by Sarepta Therapeutics. However, at the conclusion of this clinical study, a clinical study report will be prepared. In addition a manuscript will be prepared for publication in a reputable scientific journal under the direction of the Investigator and Sarepta Therapeutics. Sarepta Therapeutics and the Investigator intend to publish and communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by Sarepta Therapeutics, as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov once appropriate approval has been received and before the first subject is enrolled.

11.8 Investigational Product Control

An accurate record of the use of the investigational product vials for each subject and each dose must be kept. The drug receipt records at the investigational site and documentation of administration of the investigational product doses will be used together to provide drug accountability.

At the conclusion of the study, information describing the study drug supplies (e.g., lot number) and their disposition must be provided for each subject. The product accountability records must be signed by the Investigator and a copy will be collected by the Study Monitor. At the conclusion of the study, all unused investigational product vials must be returned to Sarepta Therapeutics or destroyed at the site according to the site's standard operating procedure(s).

11.8.1 Receipt of Investigational Product

An accurate record of the use of the investigational product vials for each subject and each dose must be kept. A proof of receipt, which details the quantity and description of the investigational product, will accompany the shipment from the Sponsor to the Investigator. This receipt must be signed, dated, and sent to the Sponsor or Sponsor designee within 24 hours after receipt, while retaining the original within the site pharmacy files. The Investigator must ensure that the investigational product is maintained in a controlled location, with limited access, and under appropriate storage conditions.

11.8.2 Disposition of Unused Investigational Product

All unused investigational products must be maintained under adequate storage conditions in a limited-access area. If any unused material is remaining upon completion of the study, the material will be returned to the Sponsor or destroyed only after the following has been completed:

- Accountability has been performed by a representative of the Sponsor
- An Investigational Product Returns and Destruction Form has been completed by the pharmacist or designee and a copy provided to the Sponsor

11.8.3 Product Handling and Complaints Reporting

If there are any issues during the course of the study related to the quality of the investigational product, the Investigator, clinical site pharmacist or pharmacy designee should contact the Sponsor.

12 REFERENCES

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13 APPENDICES

13.1 Appendix I: Schedule of Study Events

Activity	Screening (up to D -21)	Confinement Period																	Outpatient Follow up	
		Check in D -1	First Dose D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	Dis charge D 16	D 21	D 42
Informed consent	X																			
Demographics	X																			
Height, Weight and BMI [a]	X	X																		
Review Inclusion/Exclusion Criteria	X	X	X																	
Medical history [b]	X	X	X																	
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment [c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[d]	X	X																	X	X
Urinalysis/Urinary parameters [e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinary biomarkers [e,g]		X	X		X				X			X				X		X	X	X
12-lead ECG [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Vital signs [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [j]	X	X																X		
Serum pregnancy test [k]	X	X																	X	X
Drug Screen[l]	X	X																		
FSH test [m]	X																			
HIV, HBV and HCV serology	X																			
Chemistry panel (Full = F, Limited = L) [n]	F	F	F	F	F	L	L	L	F	L	L	F	L	L	L	F	F	F	F	F
GFR, based on MDRD equation	X	X	X						X			X				X		X	X	X
Serum cystatin C	X	X	X						X			X				X		X	X	X
Hematology	X	X	X	X	X				X			X				X			X	X
Coagulation (PT/aPTT)	X	X														X				
Plasma pharmacokinetic sampling [o]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine pharmacokinetic sampling [p]			X													X				
Dose subject [q]			X	X	X	X	X	X	X	X	X	X	X	X	X	X				

[a] Height at Screening only; height and weight should be measured with shoes off, height should be recorded in cm, weight in kg.

[b] Complete medical history at screening including past blood donation history, tobacco use, and history of previous investigational drug/device study participation. Brief medical history at check-in and immediately prior to dosing on Day 1 to capture safety findings that occur prior to subject dosing.

[c] Treatment-emergent AEs will be collected on an ongoing basis from initiation of dosing on Day 1 through completion of Day 42 (or time of early withdrawal as applicable). In addition, on dosing days (Days 1 through 14) the subject should be assessed for AEs immediately prior to and approximately 1 hour after dosing.

[d] Urine pregnancy testing is for women of childbearing potential only.

[e] When subject is confined to the unit on Days 1 through 16, urine should be obtained from first morning void.

[f] Urinalysis/urinary parameters including bilirubin, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, microscopy, urine microscopy (including RBC, WBC, bacteria, yeast, epithelial cells and other abnormalities such as casts, crystals and renal tubular epithelial cells), quantitative albumin, total protein, and creatinine.

[g] Urinary biomarkers including KIM-1, cystatin C, and β2-microglobulin, each normalized to urine creatinine.

[h] 12-lead ECG will be performed after the subject has been in the supine position for a minimum of 15 minutes. ECGs will be performed in triplicate (with at least 1 minute between each ECG) during Screening, on Day -1, and on Day 1 prior to dosing. On Dosing Days 1 through 14, ECGs will be performed a single time, approximately 1 hour after completion of dosing.

[i] Vital signs (temperature, respiratory rate, pulse and blood pressure) should be measured after a minimum of approximately 5 minutes of rest at all times. On dosing days, all vital signs will be collected pre dose and approximately 1 hour after initiation of dosing In addition, on Dosing Days 1 and 2, blood pressure will be measured 10 and 30 minutes after initiation of dosing; continued measurement of blood pressure at 10 and 30 minutes after initiation of dosing after Day 2 is at the discretion of the Investigator. On Days 15 and 16, vital signs should be measured approximately 24 and 48 hours after the last dose of study drug on Day 14. Temperature should be collected orally and recorded in degrees Celsius (°C).

[j] Complete physical examinations include assessment of general appearance; skin; lymph nodes; HEENT; chest/lungs; cardiovascular; abdomen; musculoskeletal; and neurological. Note that focused physical examinations may be performed throughout the study as needed (e.g., to obtain further information related to an AE).

[k] Serum pregnancy testing is for women of childbearing potential only.

[l] Includes screen for use of alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, nicotine and cotinine; urine and/or blood testing may be performed according to the means available to the Phase 1 unit; if urine is used samples will be obtained prior to ECG.

[m] Follicle Stimulating Hormone (FSH) test performed on female subjects only to confirm post-menopausal status, as applicable.

[n] Full chemistry panel includes sodium, potassium, chloride, BUN, creatinine, calcium, glucose, ALT, AST, GGT, alkaline phosphatase, lactate dehydrogenase, total bilirubin, amylase, albumin, total protein, cholesterol, and uric acid. Limited chemistry panel includes BUN and creatinine.

[o] Full plasma PK sampling will be performed at the following time points on Day 1: immediately pre-dose, at approximately 10 and 30 minutes after completion of dosing, and at approximately 1, 1.5, 2, 4, 6, 8 12, 16, and 24 hours after completion of dosing (collection of plasma 24-hours post dose will also serve as the trough sample for dose 1). Plasma PK sampling will also be performed at the following time points on Day 14: immediately pre-dose, at approximately 10 and 30 minutes after completion of dosing, and at approximately 1, 1.5, 2, 4, 6, 8 12, 16, 24, 28, 32,

36, and 48 hours after completion of dosing. Plasma sampling will also be performed immediately prior to dosing on Days 3 through 13 for determination of trough values.

[p] Urine for PK sampling will be collected during the following time intervals on Day 1 and Day 14: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after initiation of dosing. Subject will void within 30 minutes before dosing to empty bladder pre-dose, and then at 4, 8, 12 and 24 hours after initiation of dosing to complete the preceding urine collection interval.

[q] Blinded study drug (AVI-7288 or placebo) administered by IV infusion over 30 minutes, starting at approximately the same clock time of dosing on Day 1.

13.2 Appendix II: Requisite Documents for Approval of Study Site

Clinical study material will be provided to the Investigators after they have submitted the following documents to the Study Monitor:

- Signed protocol and amendment(s), if applicable
- Signed Statement of the Investigator (From FDA 1572)
- Document indicating IRB review and approval of the final protocol and the informed consent document (to include name, address, and chairperson of the IRB)
- IRB committee composition as evidenced by documentation presented by the IRB
- Blank (unsigned) copy of the IRB-approved informed consent document
- Signed Investigator's Agreement and Letter of Confidentiality
- Clinical laboratory certification and normal ranges for tests that are performed in the laboratory for study assessments
- Curricula vitae for the Investigator and Sub-Investigator(s)
- Financial disclosure information for the Investigator and Sub-Investigator(s)

13.3 Appendix III: Responsibilities of Sponsors and Investigators

13.3.1 Sponsor (Sarepta Therapeutics):

Sarepta Therapeutics or designee will conduct a pre-investigation Site Selection Visit and/or Study Initiation Visit to:

- Establish the acceptability of the facility and staff and record the visit in a written report (i.e., memorandum or form) before study initiation.
- Discuss with the Investigator the proposed clinical study and supply them with the Investigator's Brochure and the draft protocol for their review and approval.
- Discuss with the Investigator the regulatory requirements with respect to informed consent, IRB approval of the protocol, protocol amendments, and changes to the informed consent document.
- Discuss with the Investigator their obligation to supply the Study Monitor with all study-related source documents (including IRB approval, IRB charter or equivalent, IRB membership and qualifications, protocol amendments, informed consent document, and consent changes), and all pertinent correspondence to and from the IRB.

Sarepta Therapeutics or designee will conduct periodic on-site visit(s) to:

- Assure adherence to the protocol and applicable regulatory requirements.
- Review eCRFs and source documentation (e.g., clinic records) for accuracy and completeness of information.
- Examine pharmacy records for documentation of quantity and date of receipt of investigational drug, dispensation, and accountability data for product administration to each subject, loss of materials, contamination, and unused supplies.
- Record and report (summarize) observations on the progress of the study and continued acceptability of the facilities and staff, and prepare an on-site visit report.
- Review Investigator files for required documents (e.g., protocols; protocol amendments; Investigator's Brochure; IRB approval of protocols, amendments, and informed consent document; IRB membership; and communications to and from the IRB and the Study Monitor).

13.3.2 Investigator:

The Investigator must assure the Sponsor that the IRB:

- Has the authority delegated by the parent institution and found in the IRB by-laws, operation guidelines, or charter to approve or disapprove clinical studies and protocols,

including informed consent and other documents (e.g., protocol amendments and information to be supplied to subjects concerning informed consent).

- Complies with proper personnel make-up of the IRB as specified in 21 CFR 56.107.

- Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them.

- Maintains files that contain (a) documentation of its decisions, such as are found in IRB minutes and correspondence, (b) written guidelines or by-laws governing IRB functions, (c) protocol, (d) protocol amendments, (e) approved informed consent document and other information to be supplied to the subject, and (f) correspondence between the IRB and Investigator (e.g., consent changes, protocol amendments).

The Investigator must assure the Sponsor that the informed consent document for a subject:

- Includes the basic elements and any additional elements of informed consent that are appropriate in accordance with 21 CFR 50.25.

- Meets ICH guidelines as defined in ICH E6 Section 4.8: Informed Consent of Study Subjects.

- Has been approved by the IRB, including (when required) information to be given to the subject regarding the study in which he is enrolled.

- Has been signed and dated by the subject, a trained staff member who obtains consent, and the Investigator, and that a copy has been given to the subject.

The Investigator (or designated pharmacist) must assure the Sponsor that:

- Adequate and accurate written records show receipt, dispensation, and disposition of all product supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each subject.

- Purpose and reasons are given in written records for product disposal (e.g., the amount contaminated, broken, or lost) and the quantity that was returned to the Sponsor.

The Investigator must assure the Sponsor that:

- The completed eCRF accurately reflects the clinical records and original source documents for each subject.

- The eCRFs, source documentation, and clinical records will be accessible to the Study Monitor at all times.

The Investigator must assure the quality, integrity, and content of his or her files, which will be subject to review by the Study Monitor and the appropriate regulatory authority inspectors. The files must contain, at a minimum the following:

- Investigator's Brochure
- Investigator's Obligations in the US, including the following:
  - 21 CFR Part 312.60-62, 64, 66, and 68 (Responsibilities of Investigator).
  - 21 CFR Part 50 (Protection of Human Subjects)
  - International Conference on Harmonisation, GCP, Consolidated Guidelines (E6)
- IRB-approved protocol and protocol amendments
- Blank eCRFs (screen shots and amendments to eCRF)
- Statement of Investigator Forms (copy of signed Form FDA 1572, and a copy of each revised form if required by the regulatory agency) and current curricula vitae and financial disclosure information for each Investigator and Sub-Investigator
- IRB documents including the following:
  - IRB membership, and qualifications of each member
  - IRB letter of approval of protocol and informed consent form and letters of approval of protocol and informed consent form amendments
  - Investigator's continuing review (at a minimum annual report) to the IRB
  - IRB continuing review and approval of protocol
  - Reports to IRB of deaths and SAEs
  - Notification to IRB of study completion and Investigator's final report
  - IRB approval of advertisements for subject recruitment (if applicable)
  - All additional correspondence with the IRB
- IRB-approved informed consent document (all versions) and information to be supplied to the subject
- Study Staff Delegation of Authority Log
- Subject accountability records including the following:

  - Subject screening log
  - Subject identification code list (screening and randomization number as applicable)
  - Original signed informed consent documents
  - A note stating the location of the physical storage media (CD-ROM, USB flash drive, etc.) containing the eCRFs and eDCRs

- Clinical study material records including the following:
  - Receipt date, quantity, and batch or lot number
  - Disposition dates and quantity administered to each subject.
  - Inventory records (including temperature log if relevant to storage requirements)
  - All correspondence related to clinical study material

- Serious Adverse Events/Safety Reports
  - Copies of signed Serious Adverse Event Reporting Forms
  - All correspondence concerning SAEs, including the MedWatch Form FDA 3500A

- Biological sample inventory forms and correspondence with the analytical laboratory

- Monitoring activities
  - Monitoring Log (should include all visits [i.e., study site initiation, periodic, and termination visits])
  - Telephone contact reports
  - Site initiation visit reports and general correspondence
  - All correspondence between the Study Monitor, Sponsor, and the site
  - All correspondence within the site concerning the protocol

- Documents and records must be retained by the Investigator:
  - At study completion all eCRF data will be copied onto a non-rewritable CD-ROM. This disc will be presented to the Investigator. The supporting documentation and administrative records all must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the

application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

- In compliance with ICH E6, essential documents should be retained until 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 investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No study documents will be destroyed or moved to a new location without prior written notification of and approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records that are required to be maintained for the study should be transferred to an agreed-upon designee.

- Audit trails for electronic documents must be retained for a period at least as long as that required for the subject electronic records to which they pertain. The Investigator must retain either the original or a certified copy of audit trails.

13.4 Appendix IV: Confidentiality and Investigator Statement

7288-us-101

"A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers"

The information contained in this protocol and all other information relevant to 7288-us-101 are the confidential and proprietary information of Sarepta Therapeutics and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Sarepta Therapeutics.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Sarepta Therapeutics or specified designees. I will discuss the material with them to ensure that they are fully informed about AVI-7288 and the study.

_____	_____
Principal Investigator Name (printed)	Signature
_____ _____	_____
Date	Site Number

13.5 Appendix V: Additional Study Information

Study Center

SNBL Clinical Pharmacology Center, Inc. (SNBL) is a Phase 1 facility located in Baltimore, Maryland. SNBL has a separate subject waiting room, 5 examination rooms and 2 PK laboratory rooms, each with a centrifuge, -20°C and -70°C freezers. SNBL has the capacity to hold 96 inpatient subjects in 2 confinement areas. The facility is equipped with (Phillips) blood pressure and 12-lead ECG machines, (Baxter 6201) IV pumps, a wireless telemetry machine that can monitor up to 16 subjects (in one of the confinement areas), a (Phillips) pulse oximetry machine/monitor, and a weight/height scale.

The site is also equipped with 2 crash carts, all shift RN's are both Basic Life Support Training (BCLS) and Advanced Cardiac Life Support training (ACLS) certified. In addition, SNBL hires RNs exclusively with critical care experience. If they use PRN or agency trained RNs these requirements still apply. SNBL non-clinical staff also are trained in BCLS. SNBL is able to maintain ICU conditions for a short period of time while calling 911 and awaiting transfer to the local hospital, which is only one block away. All equipment is inspected and calibrated regularly. All source documents, the regulatory binder and other study documents are kept inside a secured data records room.

All investigational products are stored under the appropriate environmental conditions in a secure location in the SNBL-CPC Pharmacy. All investigational products have a dedicated space in the pharmacy to avoid trial contamination and are stored in a locked cabinet or a locked refrigerator in the pharmacy. The environmental conditions of the pharmacy and the temperature of the refrigerator located in the pharmacy are monitored by the REES Scientific Monitoring System.

Access to the Pharmacy is restricted to the pharmacy staff **only** and access is controlled via proxy card through the REES Scientific Monitoring System.

Key Study Personnel

Key study personnel and their roles and responsibilities are listed below.

Personnel	Role	Responsibilities
Mohamed Al-Ibrahim, MB ChB, FACP, SNBL Clinical Pharmacology Center 800 West Baltimore Street, 5F Baltimore MD 21201 Tel: 800-690-9110 Mobile: 410 245-6888 Fax: 410 706 8963 Email: Mal-ibrahim@snbl-cpc.com	Principal Investigator	Recruitment Informed consent Screening Medical history Physical examination Evaluation of adverse events Review of clinical laboratory results Review of entry criteria / Determination of eligibility Query resolution IRB correspondence CRF sign-off Administration of investigational product
Dr. Robert Ammlung SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 or 410-706-8812 Fax: 410-706-8963 Email: rammlung@snbl-cpc.com	Sub-investigator	Recruitment Informed consent Screening Medical history Physical examination Evaluation of adverse events Review of clinical laboratory results Review of entry criteria Query resolution IRB correspondence Administration of investigational product
Masaru Kaneko, MD, CPI SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: mkaneko@snbl-cpc.com	Sub-investigator	Recruitment Informed consent Screening Medical history Physical examination Evaluation of adverse events Review of clinical laboratory results Review of entry criteria Query resolution Administration of investigational product
Albert Fuzayl, PA, SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: afuzayl@snbl-cpc.com	Sub-investigator	Recruitment Informed consent Screening Medical history Physical examination Evaluation of adverse events Review of clinical laboratory results Review of entry criteria Query resolution Administration of investigational product

Personnel	Role	Responsibilities
Will Leslie SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: wleslie@snbl-cpc.com	Project Manager (Primary Site Contact)	Obtain Consent Notify P.I. of abnormal lab results Specimen processing Shipment of samples Complete CRFs Dispense meals Update essential documents Administrative duties Recruiting/telephone screening Trainer Recruitment Informed consent Screening Conduct of study procedures (ECG, vital signs, phlebotomy) CRF completion Query resolution
Ana Lorenzo SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201Tel: 800-690-9110 Fax: 410-706-8964 Email: alorenzo@snbl-cpc.com	Study coordinator	Recruitment Informed consent Screening Conduct of study procedures (ECG, vital signs, phlebotomy) CRF completion Query resolution Update essential documents
Rochelle Rogers, PharmDSNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: rrogers@snbl-cpc.com	Pharmacist	Study drug accountability Study drug preparation Verification of study drug Study drug dispensing
Pia Mikkelsen Lynch, MD	Independent Study Monitor	Has authority to stop the research protocol in progress, remove individual human subjects from the study, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; Reports any observations and findings to the IRB or other designated official and the HRPO; May discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research; May also observe or review recruitment, enrollment, the consent process, study interventions and interactions, monitoring plans, data collection and analysis

In the event that the key study personnel listed are unable to fulfill the roles and responsibilities listed above, a qualified alternate will be assigned. Other study responsibilities, such as study monitoring and data analysis, have been delegated to the Contract Research Organization by the Sponsor.

Study Recruitment

Prospective subjects will learn about the opportunity to participate in this trial primarily through their registration in the clinic database, but also through general information about early phase studies on the clinic internet site, and advertising media in the community such as newspaper, radio, television, and billboards. The phone screen script that will be used to call prospective subjects from the clinic database will be preapproved by the IRB. Candidates who call the recruitment center will be asked a series of questions related to basic study inclusion/exclusion criteria. Subjects who meet basic study requirements discussed during the phone screening will then be offered a screening appointment at the clinic.

Before any screening procedures are performed at the clinic, candidates will be consented using the current IRB-approved informed consent form. Subjects will then be tested by investigator-delegated staff to determine if they meet the study inclusion/exclusion criteria outlined in the protocol. The Investigator or Sub-Investigator will review the screening results, and subjects who pass all screening criteria may then be invited to participate in the study.

Consent Process

The consent process will afford potential subjects complete privacy and adequate time for decision-making.

Subject Compensation

Subjects enrolled in this study will be compensated for study participation. The compensation plan will be reviewed by the IRB, who will ensure that the compensation plan is fair and does not provide undue inducement. The detailed, prorated compensation plan will be outlined in the IRB-approved informed consent.

Study Laboratories

The following laboratories will be performing the study evaluations. No samples will be kept for future use. The samples will be analyzed and disposed as per the individual laboratory policy and procedures.

Laboratory	Evaluations
SNBL Clinical Pharmacology Center, Inc. Clinical Laboratories 800 West Baltimore Street 5th and 6th Floor Baltimore, Maryland 21201	HBV, HCV and HIV serologies Core chemistry tests Core hematology tests Urinalysis Standard urinary parameters PT/aPTT Serum pregnancy test
Helix Diagnostics Inc. 505 South Rosa Road #30A Madison, WI 53719-1276	Plasma and urine AVI-7288 levels
Esoterix Clinical Trials Service 750 Walnut Avenue Cranford, New Jersey 07016	B2 Microglobulin
Laboratory Corporation of America 1447 York Court Burlington, NC 27215	Serum cystatin C (samples will be shipped from study site to Burlington NC via Cranford NJ).
Esoterix Clinical Trials Services 5300 McConnell Ave. Los Angeles, CA 90066	Urine cystatin C KIM 1

All primary data, or copies thereof (e.g., laboratory records, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the study site archives and may be reviewed by the United States Army Medical Research and Material Command.

Continuing Review and Final Report

A copy of the approved continuing review report and the local IRB approval notification will be submitted to the Human Research Protection Office (HRPO) as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the HRPO as soon as these documents become available.

Sensitive Information

Disclosure of sensitive information about potential study participants including positive HIV, hepatitis, or tuberculosis test results, illegal residency, child or spousal abuse, or participation in other illegal activities will be handled in accordance with applicable State Law.

SUMMARY OF CHANGES

DRUG:	AVI-7288
PROTOCOL NUMBER:	7288-us-101
PROTOCOL TITLE:	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers
IND NUMBER:	101,939
SPONSOR:	Sarepta Therapeutics, Inc. 215 First Street, Suite 7 Cambridge, MA 02142 USA Phone: (857) 242-3700
CURRENT VERSION (DATE)	06 (30 July 2013)
PRIOR VERSIONS (DATES)	05 (26 March 2013) 04 (31 January 2013) 03 (17 July 2012) 02 (14 June 2012) 01 (6 June 2012) 00 (30 March 2012)

CONFIDENTIALITY STATEMENT

Substantive changes to the protocol are summarized in the table below. All changes, including minor clarifications, are included in the redline document comparing the current amendment (Version 06) with the previous amendment (Version 05) that follows.

Change/Rationale	**Protocol Section(s) Affected**
1. Add a fifth dose cohort of 8 subjects (6 active, 2 placebo) at 16 mg/kg to further define the maximum tolerated dose of AVI-7288 in humans, increasing the number of dosed subjects from 32 to 40.	• Study Synopsis • 1 Introduction, Purpose of Study • 3.2 Study Design • 5.1.5 Preparation and Administration of the Investigational Product • 5.2.1 Dose Selection Rationale • 5.2.2 Dose Escalation
2. Increase the number of subjects to be screened from 100 to 130 to identify the additional subjects for the fifth dose cohort.	• Study Synopsis • 5.4 Method of Assigning Subjects to Treatment
3. Clarify that a retest statement will be included on the label and that AVI-7288 Drug Product will be shipped in a validated shipper.	• 5.1.3 Packaging and Labeling • 5.1.4 Storage
4. Clarify that spare subjects who are not who are not dosed on a given day may remain in the unit overnight and not undergo any additional procedures, in anticipation of repeating Day -1 evaluations the following day for inclusion in the cohort.	• 5.4 Method of Assigning Subjects to Treatment
5. Clarify that routine physical examinations will be performed prior to the blood draw.	• 6.4.2 Safety Assessments
6. Clarify that post-dose ECGs will be performed approximately one hour after <u>completion of dosing</u>.	• 6.4.2.3 Electrocardiogram • Appendix I, Schedule of Study Events
7. Clarify timing of measurement of vital signs relative to initiation or completion of dosing.	• 6.4.2.4 Vital Signs • Appendix I, Schedule of Study Events

8. Clarify timing of plasma and urine PK sample collection relative to initiation of completion of dosing.	• 6.5 Pharmacokinetic Assessments • Appendix I, Schedule of Study Events
9. Clarify that amylase is one of the analytes in the full chemistry panel.	• Appendix I, Schedule of Study Events

In addition, the following administrative changes were made to the protocol:

Change/Rationale	**Protocol Section(s) Affected**
1. Change the address for Sarepta Therapeutics, Inc., as corporate headquarters have moved to Cambridge, MA.	• Title page • Clinical Protocol Approval Form • Study Synopsis
2. Add ICH Guideline for Good Clinical Practice E6 to list of references	• 12 References
3. Update study personnel to indicate that Albert Fuzayl, PA is a new sub-investigator, that Will Leslie has replaced Patrick Wilcox as project manager and that Ana Lorenzo has replaced Ashley Bathgate as study coordinator.	• Appendix V, Key Study Personnel

SUMMARY OF CHANGES

DRUG:	AVI-7288
PROTOCOL NUMBER:	7288-us-101
PROTOCOL TITLE:	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers
IND NUMBER:	101,939
SPONSOR:	Sarepta Therapeutics 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933
CURRENT VERSION (DATE)	05 (26 March 2013)
PRIOR VERSIONS (DATES)	04 (31 January 2013) 03 (17 July 2012) 02 (14 June 2012) 01 (6 June 2012) 00 (30 March 2012)

CONFIDENTIALITY STATEMENT

Protocol Version 05 incorporated one administrative change, as noted in the table below.

Change/Rationale	**Protocol Section(s) Affected**
1. Correct version numbers in protocol so that the document is consistently referred to by a single version number (Version 5).	• Title page • Clinical protocol approval form • Header – all pages

SUMMARY OF CHANGES

DRUG:	AVI-7288
PROTOCOL NUMBER:	7288-us-101
PROTOCOL TITLE:	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers
IND NUMBER:	101,939
SPONSOR:	Sarepta Therapeutics 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933
CURRENT VERSION (DATE)	04 (31 January 2013)
PRIOR VERSIONS (DATES)	03 (17 July 2012) 02 (14 June 2012) 01 (6 June 2012) 00 (30 March 2012)

CONFIDENTIALITY STATEMENT

Substantive changes to the protocol are summarized in the table below. All changes, including minor clarifications, are included in the redline document comparing the current amendment (Version 04) with the previous amendment (Version 03) that follows.

Change/Rationale	**Protocol Section(s) Affected**
1. Change the top dose to be evaluated in this multiple ascending dose study from 9 mg/kg to 12 mg/kg to encompass a dose expected to provide efficacious exposure, based on the results of the nonhuman primate pharmacokinetic (PK)/pharmacodynamic (PD) study, 7288-pkd-001.	• Study Synopsis • 1 Introduction, Purpose of Study • 3.2 Study Design • 5.1.5 Preparation and Administration of the Investigational Product • 5.2.1 Dose Selection Rationale • 5.2.2 Dose Escalation
2. Adjust the dose escalation scheme from 1, 3, 6, and 9 mg/kg to 1, 4, 8, and 12 mg/kg so that it proceeds rapidly initially and then slows to reach the efficacious exposure. Dose escalation will still be overseen by an independent Data Safety Monitoring Board.	• Study Synopsis • 1 Introduction, Purpose of Study • 3.2 Study Design • 5.1.5 Preparation and Administration of the Investigational Product • 5.2.1 Dose Selection Rationale • 5.2.2 Dose Escalation
3. Add preliminary results of the nonhuman primate PK/PD study (7288-pkd-001) to provide the rationale for the top dose to be evaluated in this multiple ascending dose study.	• 1 Introduction, Nonclincal Experience with AVI-7288 • 5.2.1 Dose Selection Rationale
4. Update study personnel to indicate that Ashley Bathgate has replaced Anastasia Dolgovskij as study coordinator and that Rochelle Rogers has replaces Olajumoke Allison as pharmacist.	• Appendix V, Key Study Personnel
5. Add table to Introduction to indicate that the species *Marburg marburgvirus* has been expanded to include Ravn virus	• 1 Introduction, Marburg Hemorrhagic Fever

CLINICAL STUDY PROTOCOL
SUMMARY OF CHANGES

DRUG:	AVI-7288
PROTOCOL NUMBER:	7288-us-101
PROTOCOL TITLE:	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers
IND NUMBER:	101,939
SPONSOR:	Sarepta Therapeutics 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933
PREVIOUS VERSION NUMBER:	02 (14 June 2012)
NEW VERSION NUMBER:	03 (17 July 2012)

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers	
Protocol Number: 7288-us-101	**Version No.:** 03
Prior Version (Date): 02 (14 June 2012)	**Version Date:** 17 July 2012

Summary of Changes:

Substantive changes to the protocol are summarized here, and then examples of these changes, their location within the protocol, and brief rationales for these changes are noted in the remainder of this document. Only newly modified text is presented in this summary document; added text is underlined, while removed text is shown in ~~strikethrough~~. In cases where the same substantive change was made in multiple sections, but with slight variations in wording, a sample of the substantive change is provided. Note that stylistic and formatting changes that do not alter the conduct of the study are not typically summarized in this document. Examples of such changes include corrections to capitalization, spelling and grammar; changes for consistency in number formatting and acronyms; and minor editing to improve clarity.

Summary of Substantive Changes to Protocol 7288-us-101 in Version 03:

The Sponsor's name changed from AVI BioPharma Inc. to Sarepta Therapeutics on 12 July 2012 and the protocol was updated accordingly. In addition, the version and date of protocol were changed to Version 3, 17 July 2012. Dr. Mohamed Al-Ibrahim replaced Dr. Rudin as the Principal Investigator for this study because Dr. Rudin left SNBL Clinical Pharmacology Center to pursue another opportunity. Dr. Al-Ibrahim was a sub-investigator for this study under prior versions of the protocol and has been replaced in that capacity by Dr. Ammlung. Information regarding the evaluation of reticulocytes, complement levels, and C3 and C4 levels was deleted from the protocol as these parameters will not be evaluated as part of this protocol. In addition, under this amendment, serum cystatin C will be evaluated by Lab Corp rather than Esoterix.

1. Location	Description of Change(s):
Header, Global	AVI-7288 Clinical Study Protocol 7288-us-101 Version ~~02~~03
Rationale/Justification for Change(s):	
Version of protocol updated.	

2. Location	Description of Change(s):
Cover Page, Global	~~AVI BioPharma, Inc.~~ Sarepta Therapeutics
Rationale/Justification for Change(s):	
The Sponsor's name was changed from AVI BioPharma Inc. to Sarepta Therapeutics on 12 July 2012 and the protocol was updated accordingly.	

2. Location	Description of Change(s):	
Cover Page, Clinical Protocol Approval Form	**CURRENT VERSION (DATE)**	~~02 (14 June~~03 (17 July 2012)
	PRIOR VERSIONS (DATES)	02 (14 June 2012)
		01 (6 June 2012)
		00 (30 March 2012)
Rationale/Justification for Change(s):		
The date and version of the protocol were updated to Version 3, 17 July 2012.		

3. Location	Description of Change(s):
Appendix V, Table of Key Study Personnel	

Personnel	Role	Responsibilities
~~Dan Rudin, MD~~ Mohamed Al-Ibrahim, MB ChB, FACP, SNBL Clinical Pharmacology ~~Ctr~~ Center 800 West Baltimore ~~St~~ Street, 5F Baltimore, MD 21201 Tel: 800-690-9110 Mobile: 410 245-6888 Fax: 410-706-8963 Email: ~~Email: drudin~~ Mal-ibrahim@snbl-cpc.com	Principal Investigator	Recruitment Informed consent Screening Medical history Physical examination Evaluation of adverse events Review of clinical laboratory results Review of entry criteria / Determination of eligibility Query resolution IRB correspondence CRF sign-off Administration of investigational product
~~Mohamed Al-Ibrahim, MB ChB, FACP~~ Dr. Robert Ammlung SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 or 410-706-8812 Fax: 410-706-8963 Email: rammlung@snbl-cpc.com~~Mal-ibrahim@snbl-cpc.com~~	Sub-investigator	Recruitment Informed consent Screening Medical history Physical examination Evaluation of adverse events Review of clinical laboratory results Review of entry criteria Query resolution IRB correspondence Administration of investigational product

Rationale/Justification for Change(s):

Dr. Al-Ibrahim, previously a sub-investigator for this study, became Principal Investigator for the study after Dr. Rudin left SNBL Clinical Pharmacology to pursue an opportunity in another state. Dr. Al-Ibrahim will be replaced as sub-investigator by Dr. Ammlung.

4. Location	Description of Change(s):
Appendix V, Table of Laboratories and Evaluations	

Laboratory	Evaluations
SNBL Clinical Pharmacology Center, Inc. Clinical Laboratories 800 West Baltimore Street 5th and 6th Floor Baltimore, Maryland 21201	HBV, HCV and HIV serologies Core chemistry tests Core hematology tests Urinalysis Standard urinary parameters PT/aPTT ~~Reticulocyte count~~ ~~Complement levels~~ Serum pregnancy test
~~Quest Diagnostics Incorporated~~ ~~1901 Sulphur Spring Road~~ ~~Baltimore, Maryland 21227~~	~~C3 and C4~~
Helix Diagnostics Inc. 505 South Rosa Road #30A Madison, WI 53719-1276	Plasma and urine AVI-7288 levels
Esoterix Clinical Trials Service 750 Walnut Avenue Cranford, New Jersey 07016	B2 Microglobulin
Laboratory Corporation of America 1447 York Court Burlington,NC 27215	Serum cystatin C (samples will be shipped from study site to Burlington NC via Cranford NJ).
Esoterix Clinical Trials Services 5300 McConnell Ave. Los Angeles, CA 90066	Urine ~~and serum~~ cystatin C KIM 1

Rationale/Justification for Change(s):

Information regarding the evaluation of reticulocytes, complement levels, and C3 and C4 levels was deleted from Appendix V as these parameters will not be evaluated as part of this protocol. In addition, under this amendment, serum cystatin C will be evaluated by Lab Corp rather than Esoterix.

CLINICAL STUDY PROTOCOL
SUMMARY OF CHANGES

DRUG:	AVI-7288
PROTOCOL NUMBER:	7288-us-101
PROTOCOL TITLE:	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers
IND NUMBER:	101,939
SPONSOR:	AVI BioPharma, Inc. 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933
PREVIOUS VERSION NUMBER:	01 (6 June 2012)
NEW VERSION NUMBER:	02 (14 June 2012)

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers	
Protocol Number: 7288-us-101	**Version No.:** 02
Prior Version (Date): 6 June 2012	**Version Date:** 14 June 2012

Summary of Changes:

Substantive changes to the protocol are summarized here, and then examples of these changes, their location within the protocol, and brief rationales for these changes are noted in the remainder of this document. Only newly modified text is presented in this summary document; added text is underlined, while removed text is shown in ~~strikethrough~~. In cases where the same substantive change was made in multiple sections, but with slight variations in wording, a sample of the substantive change is provided. Note that stylistic and formatting changes that do not alter the conduct of the study are not typically summarized in this document. Examples of such changes include corrections to capitalization, spelling and grammar; changes for consistency in number formatting and acronyms; and minor editing to improve clarity.

Summary of Substantive Changes to Protocol 7288-us-101 in Version 02:

The cover page, Sponsor signature page, headers, footers, and level 1 headings were updated for consistency with the Sponsor's new protocol template. In the new template, the Introduction Section is numbered "1", whereas in the prior version of the protocol, the Introduction Section was numbered "4". As a consequence of this change, all level 1 headings have been reduced by 3 in the current version of the protocol.

The dose levels of AVI-7288 to be administered in this study have been reduced from 3,6,9, and 15 mg/kg to 1,3,6, and 9 mg/kg (in sequential dosing cohorts). This change was made to comply with feedback on the protocol from the US Food and Drug Administration (FDA) and to better ensure the safety of participating subjects. Also in response to FDA feedback, scheduled evaluations of serum cystatin C and glomerular filtration rate (GFR) have been added to the safety assessments; additional time points for other safety assessments (urinalysis, urinary parameters, urinary biomarkers and pregnancy tests) were added; and the individual and cohort stopping rules were made more stringent. Under the current version of the protocol, a confirmed increase ≥ 1.5 fold in serum creatinine levels or a confirmed decrease in GFR to < 70 ml/min will result in, at a minimum, suspension of dosing for the individual subject. In addition, if 2 or more subjects meet these criteria within a cohort, dosing will be interrupted to allow for an ad hoc review of cumulative safety data by the Data Safety Monitoring Board (DSMB). These changes necessitated alterations to the criteria for defining the maximum tolerated dose (MTD), and the addition of these parameters to the planned safety analyses.

The entry criteria were also modified in response to FDA feedback and to better ensure the health and safety of study participants. Under the new entry criteria, subjects with a GFR < 90 will be excluded from the study. A definition of chronic health conditions and allowable medical conditions was added. Female subjects of childbearing potential are now required to use 2 forms of barrier contraception, and a definition of women of non-childbearing potential was added. In addition, male participants must now agree to use contraception for the duration of the study and for 90 days post last dose, and male participants must agree to not donate sperm for 90 days post last dose.

The study duration was corrected to be 63 days (instead of 64 as was previously written) and the fact that the check-in day (Day -1) is part of the screening period (of up to 21 days) was clarified. The text indicating that safety follow-up will be performed 5 and 26 days post discharge was deleted from the protocol because it is not accurate; safety follow-up will be performed 7 and 28 days post last dose, regardless of the subject's date of discharge.

Additional changes to the protocol to increase the safety of participating subjects and/or improve the functionality of the protocol and the quality of the data collected include the following: text was added to clarify that on dosing days, post-dose ECGs will be performed 1 hour after dosing; that subjects may not use alcohol or caffeine during the confinement period; that the safety assessments in Section 6.4.2 should be conducted in the order shown and that they should be initiated prior to dosing unless otherwise noted; and that blood pressure should be checked 10 and 30 minutes post dosing following administration of

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers	
Protocol Number: 7288-us-101	**Version No.:** 02
Prior Version (Date): 6 June 2012	**Version Date:** 14 June 2012
Summary of Changes:	
study drug on Days 1 and 2. Finally, text was added under Section 6.4.2 to indicate that a brief medical history (previously referred to as an interim medical history) should be performed at check-in and prior to dosing on Day 1. This does not represent a true change to the protocol, but rather is a clarification of the intent to collect safety information after informed consent is obtained and prior to dosing as interim medical history rather than as adverse events.	

1. Location	**Description of Change(s):**
Header, Global	**Clinical Protocol Number 7288-us-101 Version ~~01~~2**
Rationale/Justification for Change(s):	
Version of protocol updated.	

2. Location	**Description of Change(s):**
Footer, Global	~~**FINAL: 30 MARCH 6 June 2012**~~ **Confidential**
Rationale/Justification for Change(s):	
Footer revised for compliance with company's new protocol template.	

3. Location	**Description of Change(s):**
Cover Page	AVIBioPharma ~~PHASE 1~~ CLINICAL STUDY PROTOCOL ~~A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers~~ ~~Protocol Number: 7288-us-101~~ ~~Version (Date): 01 (6 June 2012)~~ ~~Prior Version (Date): 00 (30 March 2012)~~ ~~IND Number: 101,939~~ DRUG: AVI-7288 PROTOCOL NUMBER: 7288-us-101 PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers IND NUMBER: 101,939 SPONSOR: AVI BioPharma, Inc. 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933 ~~Sponsor Medical Monitor:~~ ~~Alison E. Heald, MD~~ ~~Senior Director, Clinical Development~~ ~~AVI BioPharma, Inc.~~ ~~3450 Monte Villa Parkway~~ ~~Bothell, WA 98021 USA~~ CURRENT VERSION (DATE) 02 (14 June 2012)

	~~Independent Medical Monitor:~~ ~~Pia Mildelsen Lynch, MD~~ ~~Medical Monitor~~ ~~Lynch Consulting Group, Inc.~~ ~~5610 Point West Drive, Oakwood, GA 30566~~ PRIOR VERSIONS (DATES) 01 (6 June 2012) 00 (30 March 2012)
Rationale/Justification for Change(s):	
The date and version of the protocol were updated to Version 2, 14 June 2012. The format of the cover page was updated to comply with the company's new protocol template. Although the names of the Sponsor's medical monitor and the independent monitor were removed from the cover page, no changes to the identity of these individuals were made.	

4. Location	**Description of Change(s):**
Sponsor Signature Page	CLINICAL PROTOCOL APPROVAL FORM Protocol Title: ~~TITLE:~~ A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers Study No: ~~PROTOCOL NO.:~~ 7288-us-101 Current Version (Date): 02 (14 June 2102) Prior Versions (Dates): 01 (06 June 2012) 00 (30 March 2012) This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with: • The current risk-benefit evaluation of the investigational product. • The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) parts 11, 50, 54, 56, and 312 and according to applicable local requirements. The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product. Alison E. Heald, MD Senior Director, Clinical Development AVI BioPharma, Inc. 3450 Monte Villa Parkway Bothell, WA 98021 USA Date ~~I have reviewed and approved the protocol entitled "A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers."~~
Rationale/Justification for Change(s):	
The Sponsor signature page was updated to comply with the company's new protocol template.	

5. Location	Description of Change(s):
Synopsis and Section 2 (Objectives)	**OBJECTIVES:** • To evaluate the safety and tolerability of 14 once daily intravenous (IV) infusions of ascending doses of AVI-7288 compared to placebo in healthy male and female subjects • To evaluate the pharmacokinetics (PK) of 14 once daily IV infusions of ascending doses of AVI-7288 in healthy male and female subjects
Rationale/Justification for Change(s):	
The text was modified to clarify that the PK profile for all dose levels of AVI-7288 will be evaluated in this study.	

6. Location	Description of Change(s):
Synopsis and Section 3.2 (Study Design)	**METHODOLOGY:** This is a Phase 1, randomized, double blind, placebo-controlled, multiple-dose, dose-escalation study to assess the safety, tolerability, and PK of AVI-7288 in healthy adult volunteers. Up to 32 subjects will be randomized to 4 cohorts of 8 subjects each. Within each cohort, 6 subjects will receive AVI-7288 and 2 will receive placebo once daily for 14 days; subjects and study personnel will be blinded to treatment. Every effort will be made to include ~~a similar~~an equal number of male and female subjects in each cohort. Doses of AVI-7288 will be escalated in subsequent cohorts as follows: 1 mg/kg, 3 mg/kg, 6 ~~mg/kg, 9~~ mg/kg, and ~~15~~ 9 mg/kg. Cumulative safety data through Day 21 for each cohort will be reviewed by an independent Data Safety Monitoring Board (DSMB) prior to dosing of the next cohort. All subjects will be confined to the study center from 1 day prior to the first dose of AVI-7288 or placebo until 48 hours after the last dose, i.e., from Day -1 (also referred to as check-in day) through Day 16. Subjects will return to the study center for safety evaluations 7 and 28 days post last dose~~, which is 5 and 26 days post discharge (i.e.,~~ on Days 21 and 42, respectively~~).~~
Rationale/Justification for Change(s):	
The text was modified to indicate that every effort will be made to ensure an equal number of males and females are enrolled in each cohort. The doses of AVI-7288 to be administered in the study were reduced from 3,6,9, and 15 mg/kg to 1,3,6, and 9 mg/kg. This change was made to comply with feedback on the protocol from the US Food and Drug Administration (FDA) and to better ensure the safety of participating subjects. The text indicating that safety follow-up will be performed 5 and 26 days post discharge was deleted because it is not accurate; safety follow-up will be performed 7 and 28 days post last dose, regardless of the subject's discharge date.	

7. Location	Description of Change(s):
Synopsis	**NUMBER OF SUBJECTS:** Approximately 100 subjects will be screened to allow ~~a maximum of~~ 32 subjects to be randomized and dosed.
Rationale/Justification for Change(s):	
The text was modified to increase the flexibility of the protocol in the event that additional subjects need to be added to the study.	

8. Location	Description of Change(s):
Synopsis and Section 4.1 (Inclusion Criteria)	2. Body mass index 18 kg/m^2 to 35 kg/m^2, inclusive, at the time of screening and ~~Check~~ check-in (Day -1). 3. Good general health (e.g., no chronic health conditions such as hypertension, diabetes, chronic obstructive pulmonary disease, or cardiovascular disease) as determined by the Investigator. Subjects with mild seasonal allergies or benign conditions such as Gilbert's disease may be enrolled at the discretion of the Investigator. 4. Female subjects must be of non-childbearing potential or must, in conjunction with their sexual partner(s), use 2 forms of medically acceptable barrier contraception (e.g., ~~oral contraception~~, a diaphragm with spermicidal jelly in conjunction with a male condom) during the screening period and for the entire duration of ~~the~~ study participation including the 28-day ~~post last dose~~ follow-up. Non-childbearing potential is defined as postmenopausal documented by an elevated Follicle Stimulating Hormone (FSH) level or surgically sterile (e.g., tubal ligation, hysterectomy, and/or bilateral salpingo-oophorectomy). 5. Male subjects must either be sterile or agree to use, for the entire duration of the study ~~including the 28 day~~and for 90 days post last dose ~~follow up~~, a male condom and the female sexual partner must also use a medically acceptable form of birth control (e.g. oral contraceptives). 6. Male subjects must agree to not donate sperm for at least 90 days after the last infusion of study medication.

Rationale/Justification for Change(s):
The inclusion criteria were modified to comply with feedback from the FDA and study site and to better ensure the safety of participating subjects.

9. Location	**Description of Change(s):**
Synopsis and Section 4.2 (Exclusion Criteria)	13. Glomerular filtration rate (GFR) of <~~80~~ 90 mL/min, based on the Modification of Diet in Renal Disease (MDRD) equation.
Rationale/Justification for Change(s):	
Exclusion criterion 13 was modified to comply with FDA feedback and to better ensure the safety of participating subjects.	

10. Location	**Description of Change(s):**
Synopsis, Section 3.2 (Study Design), Section 5.1.5.1 (AVI-7288), and Section 5.2.1 (Dose Selection Rationale)	**DOSE/ROUTE/REGIMEN (TEST ARTICLE):** AVI-7288 is a phosphorodiamidate morpholino oligomer with positive charges (PMO*plus*™) that targets Marburg virus nucleoprotein (NP). AVI-7288 Drug Product is supplied in 5-mL vials containing 5 mL AVI-7288 at a concentration of 50 mg/mL. The dose levels of AVI-7288 for each cohort are: • Cohort 1: AVI-7288 at ~~3~~ 1 mg/kg IV • Cohort 2: AVI-7288 at ~~6~~ 3 mg/kg IV • Cohort 3: AVI-7288 at ~~9~~ 6 mg/kg IV • Cohort 4: AVI-7288 at ~~15~~ 9 mg/kg IV The amount of AVI-7288 Drug Product required to administer the required dose will be diluted to a volume of approximately 150 mL with normal saline solution (NSS) and given by IV infusion over 30 minutes once a day for 14 days. Infusions will be administered at approximately the same time each day.
Rationale/Justification for Change(s):	
The doses of AVI-7288 to be administered in the study were reduced from 3,6,9, and 15 mg/kg to 1,3,6, and 9 mg/kg to comply with FDA feedback on the protocol and to better ensure the safety of participating subjects. In addition, the text was modified to read "AVI-7288 Drug Product" for consistency with the labels on the vials of study medication supplied to the site; this change was made globally where appropriate.	

11. Location	**Description of Change(s):**
Synopsis, Section 3.2.1 (Completion of a Subject's Participation in the Study and Overall Study Completion)	**DURATION OF STUDY:** ~~Including~~ With a screening period of up to 21 days (including 1 day to check in to the study unit), 14 days of dosing, and 28 days of safety follow up post last dose, the study duration for each ~~patient~~ subject is expected to be approximately ~~64~~ 63 days. As previously noted, subjects will be confined to a study unit for 17 of these days.
Rationale/Justification for Change(s):	
Text was modified to clarify that the check-in day (Day -1) is part of the screening period. Therefore, the total duration of the study for each subject is expected to be 63 rather than 64 days.	

12. Location	Description of Change(s):
Synopsis	**CRITERIA FOR EVALUATION:** Safety and Tolerability Safety will be assessed through a review and evaluation of ~~all documented~~ adverse events (AEs), ~~drug-related AEs,~~ serious adverse events (SAEs), AEs leading to study drug discontinuation, and serial ~~observations~~clinical assessments including vital signs, physical examinations, clinical laboratory tests (hematology, chemistry and coagulation, urinalysis, standard urinary parameters, urinary biomarkers, serum cystatin C), and 12-lead ECGs. Additional safety assessments may be performed ~~if~~as deemed necessary by the Investigator. Pharmacokinetics The PK of AVI-7288 will be determined from multiple plasma and urine samples collected over 24 hours following the first administration of study drug on Day 1 and up to 48 hours following the final administration of study drug on Day 14. Trough levels will be measured on Days 2 through ~~13~~ 14. The PK parameters to be characterized include ~~but are not limited to~~ the maximum plasma concentration (C_{max}), the apparent volume of distribution at steady state (~~V_{ss}~~/V_{ss}), the elimination half-life ($t_{½}$), the time at which C_{max} occurs (~~t_{max}~~/T_{max}), area under the ~~plasma concentration~~ curve (AUC), total clearance at steady state (Cl_{ss}), mean residence time (MRT), and renal (i.e., urinary) clearance (~~Cl_R~~/Cl_R).
Rationale/Justification for Change(s):	
The text was modified to clarify that safety will be assessed via a thorough review of all adverse events. In addition, serum cystatin C will now be evaluated at regular intervals to monitor renal function. The text was also modified to clarify that trough levels of AVI-7288 will be evaluated on Days 2 through 14.	

13. Location	Description of Change(s):
Synopsis, Section 9.9 (Pharmaco-kinetic Analysis)	**STATISTICAL METHODS:** Safety: Safety and tolerability of AVI-7288 will be based upon the review of individual values and summary statistics. Incidence of treatment-emergent AEs will be tabulated by counts and percentages. Abnormalities in clinical laboratory, vital signs, and ECG will be based on pre-defined normal ranges and will be tabulated by dose group showing subject counts and percentages. Placebo-treated subjects will be pooled across all dose groups. Pharmacokinetics: Pharmacokinetic parameters will be summarized by mean, standard deviation (SD), coefficient of variation (CV), ~~and~~ minimum, and maximum for each dose level. Dose proportionality for C_{max} and AUC(s) will be assessed visually by plotting these parameters against dose. Accumulation ratios for C_{max} and AUC(s) and time to steady state will be assessed. The ~~terminal phase~~ PK profile following ~~14 days~~ the last of ~~consecutive dosing~~ 14 daily doses (Day 14 profile) will ~~also~~ be compared to that following a single dose (Day 1 profile~~.~~) to assess the within-subject impact of multiple dosing on the elimination of AVI-7288.
Rationale/Justification for Change(s):	
The text was modified to clarify that the PK profile following the last dose of AVI-7288 will be compared to that following the first dose.	

14. Location	Description of Change(s):
Section 1 (Introduction)	The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of 14 once daily intravenous (IV) infusions of AVI-7288, a potential post- exposure prophylactic treatment for patients that have documented or suspected exposure to Marburg ~~hemorrhagic fever (MHF),~~virus, compared to placebo. Four dose levels of AVI-7288 will be examined: 1, 3, 6, ~~9,~~ and ~~15~~ 9 mg/kg. 2010). Because it is highly lethal and readily transmitted from person to person, Marburg virus has been classified by the US CDC as a potential "Category A" agent of bioterrorism, and deemed of high priority~~.~~ for focused preparedness efforts, including the development of effective countermeasures to infection (CDC 2012). in the viral budding and cellular extrusion process. The addition of the positive charges to the molecule is thought to nonspecifically enhance binding to negatively charged viral RNA, possibly subverting the consequences of individual viral resistance mutations if they should evolve. AVI-7288 consists of 23 bases and contains ~~6 positive~~5 positively charged piperazinyl moieties. Its chemical name is: To date, AVI-7288 has been evaluated in clinical and nonclinical studies as a component of AVI-6003, which entails the ~~sequential~~ administration of AVI-7288 and AVI-7287, a similar
Rationale/Justification for Change(s):	
Text was modified to better reflect the proposed indication for AVI-7288. Text was added to clarify the implications of Marburg virus' identification as a category A agent of bioterrorism. Text was also added to clarify the reason for adding positive charges to the study drug (AVI-7288) and the number of positive charges in the molecule was corrected (i.e., changed from 6 to 5). The word "sequential" was eliminated from the description of the nonclinical studies because in some cases AVI-7288 and AVI-7287 were administered as a mixture (relevant details are provided in the appropriate sections of the Investigator's Brochure).	

15. Location	Description of Change(s):
Section 1.2 (Summary of Potential Benefits)	This trial is designed to characterize the safety, tolerability, and PK of multiple IV doses of AVI-7288 in healthy human volunteers. Subjects enrolled in the trial are not expected to receive any medical benefit from their participation.
Rationale/Justification for Change(s):	
"Tolerability" was added to the text above to clarify that the study will examine both the safety and tolerability of AVI-7288.	

16. Location	Description of Change(s):
Section 3.1.2 (Safety Endpoints), Section 3.3 (Discussion of Study Design)	~~5.1.2~~3.1.2 ***Safety Endpoints*** The safety and tolerability of AVI-7288 will be assessed through a review and evaluation of: • The frequency and severity of AEs, SAEs, and discontinuations due to AEs • Laboratory testing including hematology, coagulation, chemistry, urinalysis, standard urinary parameters, ~~and~~ urinary biomarkers, and serum cystatin C • Estimated GFR, based on the Modification of Diet in Renal Disease (MDRD) equation
Rationale/Justification for Change(s):	
In response to FDA feedback and to better ensure the safety of participating subjects, serum cystatin C and GFR will now be evaluated at regular intervals to monitor renal function.	

17. Location	Description of Change(s):
Section 3.2.1 (Completion of a Subject's Participation in the Study and Overall Study Completion)	~~Including a screening period of up to 21 days, 1 day to check in to the study unit, 14 days of dosing, and 28 days of safety follow-up post last dose, the study duration for each patient is expected to be approximately 64 days. As previously noted, subjects will be confined to a study unit for 17 of these days.~~
Rationale/Justification for Change(s):	
The text above was deleted from this section of the protocol because it is not relevant to the section and it occurs in other sections.	

18. Location	Description of Change(s):
Section 3.2.1.3 (Overall Study Completion)	The study will be considered to be complete when the last dosed subject has completed ~~their~~his/her Day 42 assessments (including early termination assessments) or is withdrawn from the study or is considered lost to follow-up.
Rationale/Justification for Change(s):	
Text was added to clarify the circumstances under which the study will be considered completed.	

19. Location	Description of Change(s):
Section 5.1 (Test Article)	Active drug consists of AVI-7288 formulated with phosphate buffered saline at a concentration of 50~~-~~ mg/mL ~~-~~ AVI-7288 Drug Product is supplied in aseptically filled, 5~~-~~mL vials containing 5 mL AVI-7288. It is a concentrate intended for dilution in normal saline solution (NSS) followed by IV administration.
Rationale/Justification for Change(s):	
Text added to clarify the preparation of study drug for infusion.	

20. Location	Description of Change(s):
Section 5.1.5.1 (AVI-7288) and Global	into the bag of NSS. The bag will then be labeled with the subject's ~~treatment~~randomization number, and date and time of study drug preparation.
Rationale/Justification for Change(s):	
The term "treatment number" has been corrected to read "randomization number".	

21. Location	Description of Change(s):
Section 5.2.1 (Dose Selection Rationale)	The present study will examine the safety~~, and~~, tolerability, and PK of 14 once daily IV infusions of 1, 3, 6, ~~9~~ or ~~15~~ 9 mg/kg AVI-7288, administered in sequential dose cohorts. Pharmacokinetic ~~pharmacokinetic~~PK/pharmacodynamic study. The doses selected for the current human study are intended to escalate up to and include ~~15 mg/kg~~9 mg/kg, which would encompass an efficacious exposure if doses of AVI-7288 scale from monkeys to humans based on body surface area. If the results of the upcoming PK/PD study suggest that higher doses of AVI-7288 are required to achieve efficacious exposure in humans, the protocol will be modified accordingly, to test whether exposures equivalent to or greater than that of the efficacious exposure in cynomolgus monkeys can be safely achieved~~.~~ at this dose.
Rationale/Justification for Change(s):	
Text modified to clarify that the PK profile for AVI-7288 will be evaluated in this study. Text was also added to indicate that if forthcoming data from a non human primate study suggest that higher doses of AVI-7288 might be needed to achieve the desired exposure in humans, another dosing cohort could be added to the study via protocol amendment.	

22. Location	Description of Change(s):
Section 5.2.3 (Treatment Interruption or Discontinuation)	In addition, dosing of an individual subject will be suspended and the Sponsor will be notified within 24 hours if the subject develops any of the following: • An SAE, a Grade 4 AE or a Grade 4 laboratory event, for which no clear alternative explanation, other than study drug, exists (~~grades~~Grades are according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" as noted in Section 7.2.2~~).~~) • A Grade ≥ 3 rash and/or Grade ≥ 3 allergic reaction (e.g., generalized urticaria, angioedema~~).~~) • A Grade ≥ 3 local infusion site reaction, including pain, tenderness, erythema or swelling~~.~~ • ~~Serum~~A serum creatinine ≥ Grade 2 toxicity (≥ 1.8 mg/dL~~).~~) • A confirmed ~~→~~≥ 1.5-fold increase in serum creatinine level from baseline • A confirmed decrease in GFR to < 70 mL/min, irrespective if serum creatinine is normal range or Grade 1 • A confirmed > 3~~-~~fold increase from pre~~-~~dose on Day 1 in UACR to an absolute value > 30 mg/g~~.~~
Rationale/Justification for Change(s):	
The criteria for suspending dosing in an individual subject were modified in response to FDA feedback on the protocol and to better ensure the safety of participating subjects.	

23. Location	Description of Change(s):
Section 5.2.3.1 (Cohort Stopping Rules)	In addition, dosing will be interrupted to allow for an ad hoc review of cumulative safety data by the DSMB if any of the following conditions are met within a cohort: • Two or more subjects develop the same or clinically similar Grade ≥ 3 AE or laboratory abnormality~~.~~ • Two or more subjects develop a serum creatinine ≥ Grade 2 toxicity (≥ 1.8 mg/dL~~).~~~~.~~) • Two or more subjects develop ≥ 1.5-fold increase in serum creatinine level from baseline • Two or more subjects develop GFR < 70 mL/min, irrespective if serum creatinine is normal range or Grade 1 • Two or more subjects who are not menstruating females develop a confirmed > 3~~-~~fold increase from pre~~-~~dose on Day 1 in UACR to an absolute value > 30~~-~~ mg/g~~.~~
Rationale/Justification for Change(s):	
The cohort stopping rules were modified in response to FDA feedback on the protocol and to better ensure the safety of participating subjects.	

24. Location	Description of Change(s):
Section 5.2.3.2 (Determination of the Maximum Tolerated Dose)	The maximum tolerated dose (MTD) of AVI-7288 will be the dose below the level at which ≥ 2/6 of subjects on active drug in any specific dose cohort experience any of the following: • ~~-~~Serum creatinine ≥ Grade ~~3~~2 toxicity (≥~~2~~ 1~~.~~8 mg/dL~~).~~)
Rationale/Justification for Change(s):	
The criteria for determining the MTD were modified in light of the increased stringency of the cohort stopping rules.	

25. Location	Description of Change(s):
Section 5.3 (Prior and Concomitant Medications)	The use of alcohol and caffeine is prohibited during the confinement period, i.e. from Day -1 (also referred to as check-in Day) through Day 16 The following concomitant medications may be used during the study, including during the confinement period:
Rationale/Justification for Change(s):	
Text was added to clarify that subjects may not use alcohol or caffeine during the confinement period of this study.	

26. Location	Description of Change(s):
Section 5.4 (Method of Assigning Subjects to Treatment)	To facilitate enrollment of each cohort, ~~up to 4 spare~~additional subjects may undergo Day -1 assessments simultaneously with those subject(s) designated for dosing on Day 1. These spare
Rationale/Justification for Change(s):	
Text was modified to increase the flexibility of the protocol in the event that additional subjects are required to undergo Day-1 assessments to ensure a given dosing cohort is fulfilled.	

27. Location	Description of Change(s):
Section 6.3 (Screening Assessments)	• Urine collection for pregnancy test (in ~~females as applicable~~women of childbearing potential), urinalysis, ~~urinary parameters,~~ and urinary ~~biomarkers~~parameters (see Section 6.4.2.6~~9.4.2.5~~)) • Blood collection for pregnancy ~~test~~testing in females of childbearing potential or follicle stimulating hormone (FSH) ~~test (~~testing in females to confirm post-menopausal status (as applicable), drug and alcohol screen, chemistry, hematology, coagulation, ~~and~~ serology (e.g., ~~Hepatitis B surface antigen, Hepatitis C antibody,~~ HBsAg, HCV, and HIV~~)~~), and cystatin C (see Section 6.4.2.6)
Rationale/Justification for Change(s):	
Text was modified to indicate that pregnancy testing is only applicable for women of childbearing potential (as defined in the inclusion criteria). In addition, urinary biomarkers will not be evaluated during screening; its inclusion in this section in the prior version of the protocol was in error. Text was also added to clarify that FSH testing is only required in order to confirm post-menopausal status.	

28. Location	Description of Change(s):
Section 6.4.2 (Safety Assessments)	Safety parameters will include the use of concomitant medications, physical examinations, ECGs, vital signs, clinical laboratory testing (e.g., hematology, chemistry, coagulation, urinalysis, and urinary biomarkers), and collection of AEs (from first dose as described in Section 7~~) .~~). Of note, throughout the study, the following assessments will be initiated prior to dosing (unless otherwise specified) and will be performed in the following order: • Urine collection for safety laboratory assessments, including biomarkers and pregnancy testing in females of childbearing potential • 12-lead ECG (after the subject has been lying still for at least 15 minutes~~).~~) • Vital sign measurements (to be obtained immediately after ECG recording) • Blood collection for safety laboratory assessments • Blood collection for PK testing (immediately before study treatment administration when applicable; see Section 6.5~~). Sample collection for PK testing is described in .~~)
Rationale/Justification for Change(s):	
Text was added to clarify that the safety assessments in the bulleted list should be conducted in the order shown and that they should be initiated prior to dosing unless otherwise indicated (e.g., ECGs are only performed after dosing on Days 2 through 14 as indicated in Section 6.4.2.3..	

29. Location	Description of Change(s):
6.4.2.1 (Brief Medical History)	*6.4.2.1 Brief Medical History* A brief medical history will be performed at check-in and immediately prior to dosing on Day 1 to capture safety findings that occur prior to subject dosing.
Rationale/Justification for Change(s):	
Text was added to indicate that a brief medical history (previously referred to as an interim medical history) should be performed at check-in and prior to dosing on Day 1. Any findings will be considered medical history.	

30. Location	Description of Change(s):
Section 6.4.2.3 (Electrocardio-gram)	~~a single time.~~ On dosing days, post-dose ECGs will be performed approximately 1 hour after dosing.
Rationale/Justification for Change(s):	
Text added to clarify that on dosing days, post-dose ECGs will be performed 1 hour after dosing.	

31. Location	Description of Change(s):
Section 6.4.2.4 (Vital Signs)	~~On Dosing Days 1 through 14, vital~~Vital signs will be ~~collected~~measured prior to dosing and ~~again~~ approximately 1 hour post dosing on all dosing days, as well as 24 and 48 hours after the last dose of study medication is administered. In addition, blood pressure will also be measured 10 and 30 minutes after the first and second doses of study drug are administered; continued measurement of blood pressure at 10 and 30 minutes post dosing on subsequent dosing days is at the discretion of the Investigator.
Rationale/Justification for Change(s):	
Text added to clarify the timing of vital signs assessment. In addition, blood pressure will now be monitored 10 and 30 minutes post dosing after the first and second doses of study medication are administered to provide additional safety oversight. Continued monitoring of blood pressure 10 and 30 minutes post dosing on subsequent dosing days will be at the discretion of the investigator.	

32. Location	Description of Change(s):
Section 6.4.2.5 (Physical Examination)	Complete physical examinations will be conducted at the time points specified in Appendix I: Schedule of Study Events. Physical examinations will be performed by the Investigator, an MD Sub-Investigator, a Physician's Assistant, or a Nurse Practitioner (if licensed in the state to
Rationale/Justification for Change(s):	
Text added to specify that a Physician's Assistant may conduct physical examinations for this study.	

33. Location	Description of Change(s):
Section 6.4.2.6 (Clinical Laboratory Assessments)	Additional parameters: Serum cystatin C Pregnancy testing: Urine and serum pregnancy testing ~~[a]~~Use first morning urine on days when subject is confined to the unit. [b]GFR will also be calculated based on the MDRD equation at the indicated timepoints. alteration in medical care. If clinically significant deterioration from baseline ~~(defined as the last value collected prior to dosing)~~ levels is noted, the changes will be documented in the eCRF as an AE, according to Section 7.4. The Investigator will continue to monitor the subject with additional assessments until:
Rationale/Justification for Change(s):	
In response to FDA feedback and to better ensure the safety of participating subjects, serum cystatin C and GFR will be monitored at specified time points during the study. Pregnancy testing was added to the list of laboratory assessments for completeness (its prior omission was erroneous). The definition of baseline was removed from this and all other sections of the protocol except for Section 9.1 to improve the clarity and consistency of the protocol.	

34. Location	Description of Change(s):
Section 7.6 (Pregnancy Reporting)	abortion, etc.). If it becomes known that the female partner of a male subject becomes pregnant during the treatment or follow-up period of this study, the pregnancy will be followed until the outcome of the pregnancy is known. During the follow-up period, the Investigator must report on
Rationale/Justification for Change(s):	
To better ensure subject safety and to all pertinent data regarding the effects of AVI-7288, if it becomes known that the partner of a male subject becomes pregnant during the conduct of this study, the pregnancy will now be followed until its outcome is known.	

35. Location	Description of Change(s):
Section 9.1 (General Considerations)	Baseline will be defined as the last available value before dosing, or the mean of the Day -1 and Day1 pre-dose value, as appropriate.
Rationale/Justification for Change(s):	
The definition of baseline, for the purposes of data analysis, was added to this section	

36. Location	Description of Change(s):
Section 9.8.2 (Clinical Laboratory Tests)	Changes in renal function tests will be ~~specifically~~ analyzed to identify trends that may not be readily detectable in an analysis of group mean values over time. Specifically, at each time point, the number and percentage of subjects in each cohort with Grade 1, Grade 2, Grade 3 or Grade 4 toxicity serum creatinine levels will be presented. ~~The~~In addition, the number and percentage of subjects who ~~have a >3-fold increase in UACR from predose on Day 1 to an absolute value of >30 mg/g~~meet the following criteria will ~~also~~ be presented~~.~~: • A ≥ 1.5-fold increase in serum creatinine level from baseline • A decrease in GFR to < 70 mL/min • A > 3-fold increase in UACR from baseline to an absolute value of > 30 mg/g • A > 30% increase in serum cystatin C from baseline to a level above the normal (reference) range
Rationale/Justification for Change(s):	
Under the current version of the protocol, a confirmed increase ≥ 1.5 fold in serum creatinine levels or a confirmed decrease in GFR to < 70 ml/min will result in, at a minimum, suspension of dosing for the individual subject. These changes necessitated alterations the addition of these parameters (as well as other renal related parameters) to the planned safety analyses.	

37. Location	Description of Change(s):
Section 10.3, Data Safety Monitoring Board	An independent DSMB will be assembled by the Sponsor and will consist of up to ~~4 physicians~~5 members with relevant experience and expertise (including at least 1 with expertise in
Rationale/Justification for Change(s):	
Text was added to state that the DSMB may consist of up to 5 members and that not all of them are required to by physicians. This will allow for other experts, such as statisticians, to be members of the DSMB as needed in order to better protect the safety of participating subjects.	

38. Location	Description of Change(s):
Appendix I (Schedule of Study Assessments)	**Please refer to table at end of this document.**
Rationale/Justification for Change(s):	
The schedule of study events in Appendix I was updated to reflect all of the changes in the type of assessments and in the timing of assessments described in this document.	

39. Location	Description of Change(s):
Appendix IV (Confidentiality and Investigator Statement)	13.4 Appendix IV: Confidentiality and Investigator Statement 7288-us-101 *"A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI 7288 in Healthy Adult Volunteers"* The information contained in this protocol and all other information relevant to 7288-us-101 are the confidential and proprietary information of AVI BioPharma, Inc., (AVI) and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of AVI. I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated. I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by AVI or specified designees. I will discuss the material with them to ensure that they are fully informed about AVI-7288 and the study. Principal Investigator Name (printed) Signature ~~Page~~ ~~I confirm that I have read and understand this protocol. I agree to conduct this clinical study according to the protocol, including any protocol amendments that have been mutually agreed to in writing and approved in advance by the Institutional Review Board. I also agree to conduct this study in compliance with the Principles of Good Clinical Practice as defined by federal, state, and local laws and regulations, as well as with the requirements of the appropriate Institutional Review Board, and the appropriate International Conference on Harmonization guidelines.~~ ~~Investigator Signature Date~~ ~~Investigator Name (please print or type)~~
Rationale/Justification for Change(s):	
The Investigator's signature page was updated to comply with the company's new protocol template.	

40. Location	Description of Change(s):
Appendix V (Additional Study Information)	Esoterix Clinical Trials Services 5300 McConnell Ave. Los Angeles, CA 90066 | ~~Cystatin~~Urine and serum cystatin C KIM 1
Rationale/Justification for Change(s):	
Text was added to indicated that both urine and serum cystatin C will be analyzed at Esoterix Clinical Trial Services in Los Angeles, California.	

~~15.1~~13.1 Appendix I: Schedule of Study Events

Activity	Screening (up to D ~~-~~21)	Confinement Period																Outpatient Follow up	
		Check in D ~~-~~1	First Dose D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	Dis-charge D 16	D 21	D 42
Informed consent	X																			
Demographics	X																			
Height, Weight and BMI [a]	X	X																		
Review Inclusion/Exclusion Criteria	X	X	X																	
Medical history [b]	X	X	X																	
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment [c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[d]	X	X																	X	X
Urinalysis/Urinary parameters [e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinary biomarkers [e,g]		X	X		X				X			X				X		X	X	X
12~~-~~lead ECG [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Vital signs [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [j]	X	X																X		
Serum pregnancy test [k]	X	X																	X	X
Drug Screen[l]	X	X																		
FSH test [m]	X																			
HIV, HBV and HCV serology	X																			
Chemistry panel (Full = F, Limited = L) [n]	F	F	F	F	F	L	L	L	F	L	L	~~X~~F	L	L	L	F	F	F	F	F
~~Hematology~~GFR, based on MDRD equation	X	X	X	~~X~~	~~X~~				X			X				X		X	X	X
Serum cystatin C	X	X	X						X			X				X		X	X	X
Hematology	X	X	X	X	X				X			X				X			X	X
Coagulation (PT/aPTT)	X	X														X				
Plasma pharmacokinetic sampling			~~FX~~	~~↓~~	~~↓~~	~~↓~~	~~↓~~	~~↓~~	~~↓~~	~~↓~~	~~↓~~	~~FX~~	~~FX~~	~~FX~~	~~↓~~	~~FX~~	~~FX~~	~~FX~~		

~~(Full = F, Trough = T):~~				X	X	X	X	X	X	X	X				X				
Urine pharmacokinetic sampling [p]			X													X	X		
Dose subject [q]			X	X	X	X	X	X	X	X	X	X	X	X	X	X				

[a] Height at Screening only; height and weight should be measured with shoes off, height should be recorded in cm, weight in kg.

[b] Complete medical history at screening including past blood donation history, tobacco use, and history of previous investigational drug/device study participation. ~~Interim~~Brief medical history at ~~Check-~~check-in and immediately prior to dosing on Day 1 to capture safety findings that occur prior to subject dosing.

[c] Treatment-emergent AEs will be collected on an ongoing basis from initiation of dosing on Day 1 through completion of Day 42 (or time of early withdrawal as applicable). In addition, on dosing days (Days 1 through 14) the subject should be assessed for AEs immediately prior to and approximately 1 hour after dosing.

[d] Urine pregnancy testing is for women of childbearing potential only.

[e] When subject is confined to the unit on Days 1 through 16, urine should be obtained from first morning void.

[f] Urinalysis/urinary parameters including bilirubin, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, microscopy, urine microscopy (including ~~red blood cells, white blood cells~~RBC, WBC, bacteria, yeast, epithelial cells and other abnormalities such as casts, crystals and renal tubular epithelial cells~~; Standard urinary parameters including)~~, quantitative albumin, total protein, and creatinine.

[g] Urinary biomarkers including ~~Kidney Injury Molecule-1 (~~KIM-1~~)~~, cystatin C, and β2-microglobulin, each normalized to urine creatinine.

[h] 12-lead ~~electrocardiogram (~~ECG~~)~~ will be performed after the subject has been in the supine position for a minimum of 15 minutes. ECGs will be performed in triplicate (with at least 1 minute between each ECG) during Screening, on Day -1, and on Day 1 prior to dosing. On Dosing Days 1 through 14, ECGs will be performed a single time, approximately 1 hour after dosing.

[i] Vital signs (temperature, respiratory rate, pulse and blood pressure) should be measured after a minimum of approximately 5 minutes of rest at all times. On ~~Days 1 through 14~~dosing days, all vital signs ~~should~~will be ~~measured~~collected pre-dose and ~~then~~ approximately 1 hour post-dose. In addition, on Dosing Days 1 and 2, blood pressure will be measured 10 and 30 minutes post dose; continued measurement of blood pressure at 10 and 30 minutes post dose after Day 2 is at the discretion of the Investigator. On Days 15 and 16, vital signs should be measured approximately 24 and 48 hours after the last dose of study drug on Day 14. Temperature should be collected orally and recorded in degrees Celsius (°C).

[j] Complete physical examinations include assessment of general appearance; skin; lymph nodes; ~~head, eyes, ears, nose and throat (~~HEENT~~)~~; chest/lungs; cardiovascular; abdomen; musculoskeletal; and neurological. Note that focused physical examinations may be performed throughout the study as needed (e.g., to obtain further information related to an AE).

[k] Serum pregnancy testing is for women of childbearing potential only.

[l] Includes screen for use of alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, nicotine and cotinine; urine and/or blood testing may be performed according to the means available to the Phase 1 unit; if urine is used samples will be obtained prior to ECG.

[m] Follicle Stimulating Hormone (FSH) test performed on female subjects only to confirm post-menopausal status, as applicable.

[n] Full chemistry panel includes sodium, potassium, chloride, ~~blood urea nitrogen~~BUN, creatinine, calcium, glucose, ~~alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase~~ALT, AST, GGT, alkaline phosphatase, lactate dehydrogenase, total bilirubin, albumin, total protein, cholesterol, and uric acid. Limited chemistry panel includes ~~blood urea nitrogen~~BUN and creatinine.

[o] Full plasma PK sampling will be performed at the following time points on Day 1: immediately pre-dose, at approximately 10 and 30 minutes post-dose, and at approximately 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours post-dose (collection of plasma 24-hours post dose will also serve as the trough sample for ~~Day 2).~~ dose 1). Plasma PK sampling will also be performed at the following time points on Day 14: immediately pre-dose ~~on Day 14~~, at approximately 10 and 30 minutes post-dose, and at approximately 1, 1.5, 2, 4, 6, 8 12, 16, 24, 28, 32, 36, and 48 hours post-dose ~~(collection of plasma pre-dose on Day 14 will also serve as the trough sample for that day).~~ Plasma sampling will also be performed immediately prior to dosing on Days 3 through 13 for determination of trough values.

[p] Urine for PK sampling will be collected at the following time intervals on Day 1 and Day 14: ~~pre-dose until completion of infusion,~~ 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours ~~post-dose.~~ after initiation of dosing. Subject will void within 30 minutes before dosing to empty bladder pre-dose, and then 4, 8, 12 and 24 hours ~~± 15 minutes post dose~~after initiation of dosing to complete the preceding urine collection interval.

[q] Blinded study drug (AVI-7288 or placebo) administered by IV infusion over 30 minutes, starting at approximately the same clock time of dosing on Day 1.

CLINICAL STUDY PROTOCOL
SUMMARY OF CHANGES

DRUG: AVI-7288

PROTOCOL NUMBER: 7288-us-101

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers

IND NUMBER: 101,939

SPONSOR:
AVI BioPharma, Inc.
3450 Monte Villa Parkway
Bothell, WA 98021 USA
Phone: (425) 354-5038
Fax: (425) 489-5933

PREVIOUS VERSION NUMBER:	00 (30 March 2012)
NEW VERSION NUMBER:	01 (6 June 2012)

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI 7288 in Healthy Adult Volunteers	
Protocol Number: 7288-us-101	**Version No.:** 01
Prior Version (Date): 00 (30 March 2012)	**Version Date:** 6 June 2012
Summary of Changes:	
Substantive changes to the protocol are summarized here, and then examples of these changes, their location within the protocol, and brief rationales for these changes are noted in the remainder of this document. Only newly modified text is presented in this summary document; added text is underlined, while removed text is shown in ~~strikethrough~~. Summary of Substantive Changes to Protocol 7288-us-101 in Version 01: The contact information for and responsibilities of the independent medical monitor for this study were added to the table of study-specific key personnel contained in Appendix V. The version of the protocol was changed from Version 00 to Version 01, and the date of the protocol was changed from 30 March 2012 to 6 June 2012; this is reflected in edits to the cover page and headers/footers.	

1. Location	**Description of Change(s):**
Header, Global	**Clinical Protocol Number 7288-us-101 Version 01**
Rationale/Justification for Change(s):	
Version of protocol updated.	

2. Location	**Description of Change(s):**
Footer, Global	**FINAL: ~~30 MARCH~~ 6 June 2012**
Rationale/Justification for Change(s):	
Date of protocol updated.	

3. Location	**Description of Change(s):**
Cover Page	**Protocol Number**: 7288-us-101 **~~Original~~ Version~~:~~ (Date):** 01 (6 June 2012) **Prior Version (Date):** 00 (30 March 2012)
Rationale/Justification for Change(s):	
Version and date of protocol updated.	

4. Location	**Description of Change(s):**		
Table of Key Study Personnel, Appendix V, page 78	Pia Mikkelsen Lynch, MD	Independent Study Monitor	May discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research; Has authority to stop the research protocol in progress, remove individual human subjects from the study, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; Reports any observations and findings to the IRB or other designated official and the HRPO; May also observe or review recruitment, enrollment, the consent process, study interventions and interactions, monitoring plans, data collection and analysis
Rationale/Justification for Change(s):			
Contact information for and the responsibilities of the Independent Study Monitor were added to the protocol to comply with DOD requirements of DODI 3216.02.			

PHASE 1 CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers

Protocol Number: 7288-us-101

Original Version: **30 March 2012**

IND Number: 101,939

Sponsor:	AVI BioPharma, Inc. 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933
Sponsor Medical Monitor:	Alison E. Heald, MD Senior Director, Clinical Development AVI BioPharma, Inc. 3450 Monte Villa Parkway Bothell, WA 98021 USA
Independent Medical Monitor:	Pia Mikkelsen Lynch, MD Medical Monitor Lynch Consulting Group, Inc. 5610 Point West Drive, Oakwood, GA 30566

Signature Page for Sponsor's Representative

I have reviewed and approved the protocol entitled "A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers."

A. E. Heald 02 April 2012

Date

Alison E. Heald, MD
Senior Director, Clinical Development
AVI BioPharma, Inc.
3450 Monte Villa Parkway
Bothell, WA 98021 USA

1 SYNOPSIS

NAME OF COMPANY	NAME OF FINISHED PRODUCT
AVI BioPharma, Inc. 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933	AVI-7288 Injection **NAME OF ACTIVE INGREDIENT** AVI-7288

TITLE:

A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers

PROTOCOL NO.:

7288-us-101

INVESTIGATOR STUDY SITES:

This study will be conducted at 1 study center located in the United States.

OBJECTIVES:

- To evaluate the safety and tolerability of 14 once daily intravenous (IV) infusions of ascending doses of AVI-7288 compared to placebo in healthy male and female subjects
- To evaluate the pharmacokinetics (PK) of 14 once daily doses of AVI-7288 in healthy male and female subjects

METHODOLOGY:

This is a Phase 1, randomized, double blind, placebo-controlled, multiple-dose, dose-escalation study to assess the safety, tolerability, and PK of AVI-7288 in healthy adult volunteers.

Up to 32 subjects will be randomized to 4 cohorts of 8 subjects each. Within each cohort, 6 subjects will receive AVI-7288 and 2 will receive placebo once daily for 14 days; subjects and study personnel will be blinded to treatment. Every effort will be made to include a similar number of male and female subjects in each cohort. Doses of AVI-7288 will be escalated in subsequent cohorts as follows: 3 mg/kg, 6 mg/kg, 9 mg/kg, and 15 mg/kg. Cumulative safety data through Day 21 for each cohort will be reviewed by an independent Data Safety Monitoring Board (DSMB) prior to dosing of the next cohort.

All subjects will be confined to the study center from 1 day prior to the first dose of AVI-7288 or placebo until 48 hours after the last dose, i.e., from Day -1 (also referred to as check in day) through Day 16. Subjects will return to the study center for safety evaluations 7 and 28 days post last dose, which is 5 and 26 days post-discharge (i.e., on Days 21 and 42, respectively).

NUMBER OF SUBJECTS:

Approximately 100 subjects will be screened to allow a maximum of 32 subjects to be randomized and dosed.

INCLUSION/EXCLUSION CRITERIA:

The study population for this Phase 1 multiple ascending dose study consists of healthy male and female subjects aged 18 to 50 years, inclusive, with a body mass index (BMI) of 18 to 35 kg/m^2, inclusive.

Inclusion Criteria:

A subject must meet all of the following criteria to be eligible for this study.

NAME OF COMPANY	NAME OF FINISHED PRODUCT
AVI BioPharma, Inc. 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933	AVI-7288 Injection **NAME OF ACTIVE INGREDIENT** AVI-7288

1. Man or woman 18 to 50 years of age, inclusive, at the time of screening.
2. Body mass index 18 kg/m^2 to 35 kg/m^2, inclusive, at the time of screening and Check-in (Day -1).
3. Good general health (no chronic health conditions) as determined by the Investigator.
4. Female subjects must be of non-childbearing potential or must, in conjunction with their sexual partner(s), use 2 forms of medically acceptable contraception (e.g., oral contraception in conjunction with a male condom) during the screening period and for the entire duration of the study including the 28-day post last dose follow-up.
5. Male subjects must either be sterile or agree to use, for the entire duration of the study including the 28 day post last dose follow-up, a male condom and the female sexual partner must also use a medically acceptable form of birth control (e.g. oral contraceptives).
6. Able to understand the requirements of the study, to provide written informed consent (as evidenced by signature on an informed consent document that is approved by an Institutional Review Board [IRB]), and agreeable to abiding by the study restrictions.

Exclusion Criteria:

A subject who meets any of the following criteria will be excluded from this study.

1. Pregnancy or breastfeeding.
2. A positive urine or blood screen for drugs of abuse, including alcohol.
3. Use of any tobacco- or nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to Check-in (Day -1).
4. A positive cotinine test indicating recent nicotine use.
5. Donated blood within 90 days or plasma within 30 days of first dose on Day 1.
6. Active substance abuse or any medical or psychiatric condition that could jeopardize the subject's safety or the subject's ability to comply with the protocol.
7. Use of any medications apart from vitamins, acetaminophen, or hormonal contraception within 14 days of first dose on Day 1. Subjects with mild seasonal allergies may use antihistamines at the discretion of the Investigator after approval by the Sponsor Medical Monitor.
8. Participation in any interventional clinical trial within 45 days of first dose on Day 1 (i.e., received any other investigational drug).
9. Recipient of an organ transplant (solid or hematopoietic).
10. Prolonged QT_cF interval >440 ms for males or >460 ms for females using the average of the triplicate electrocardiograms (ECGs) collected during screening, on Day -1, or just prior to dosing on Day 1.
11. Other clinically significant ECG abnormality, as determined by the Investigator.
12. Any clinically significant abnormal hematology, chemistry, coagulation, or urinalysis value, as

NAME OF COMPANY	NAME OF FINISHED PRODUCT
AVI BioPharma, Inc. 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933	AVI-7288 Injection **NAME OF ACTIVE INGREDIENT** AVI-7288

determined by the Investigator.

13. Glomerular filtration rate (GFR) of <80 mL/min, based on the Modification of Diet in Renal Disease equation.
14. Urine-albumin-to-creatinine ratio (UACR) >30 mg/g.
15. Positive test for human immunodeficiency virus (HIV-1 serology) or known HIV infection.
16. Positive result for hepatitis B surface antigen (HBsAg) or for hepatitis C virus (HCV) antibody.
17. Use of alcohol-containing foods or beverages within 72 hours prior to Check-in on Day -1.
18. Use of caffeine-containing foods or beverages within 24 hours prior to Check-in on Day -1.
19. Febrile illness or significant infection within 48 hours before administration of the first dose of study drug on Day 1.

Note: Inclusion of each subject will be reviewed with a member of AVI BioPharma Clinical Personnel prior to enrollment in the trial. Written approval from a member of AVI BioPharma Clinical Personnel is required prior to randomization.

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

AVI-7288 is a phosphorodiamidate morpholino oligomer with positive charges (PMO*plus*™) that targets Marburg virus nucleoprotein (NP). AVI-7288 is supplied in 5-mL vials containing 5 mL AVI-7288 at a concentration of 50 mg/mL. The dose levels of AVI-7288 for each cohort are:

- Cohort 1: AVI-7288 at 3 mg/kg IV
- Cohort 2: AVI-7288 at 6 mg/kg IV
- Cohort 3: AVI-7288 at 9 mg/kg IV
- Cohort 4: AVI-7288 at 15 mg/kg IV

The amount of AVI-7288 required to administer the required dose will be diluted to a volume of approximately 150 mL with normal saline solution (NSS) and given by IV infusion over 30 minutes once a day for 14 days. Infusions will be administered at approximately the same time each day.

REFERENCE TREATMENT:

Placebo control consists of approximately 150 mL NSS administered by IV infusion over 30 minutes once a day for 14 days. Infusions will be administered at approximately the same time each day.

DURATION OF STUDY:

Including a screening period of up to 21 days, 1 day to check in to the study unit, 14 days of dosing, and 28 days of safety follow-up post last dose, the study duration for each patient is expected to be approximately 64 days. As previously noted, subjects will be confined to a study unit for 17 of these days.

CRITERIA FOR EVALUATION:

NAME OF COMPANY	**NAME OF FINISHED PRODUCT**
AVI BioPharma, Inc. 3450 Monte Villa Parkway Bothell, WA 98021 USA Phone: (425) 354-5038 Fax: (425) 489-5933	AVI-7288 Injection **NAME OF ACTIVE INGREDIENT** AVI-7288

Safety and Tolerability

Safety will be assessed through a review and evaluation of all documented adverse events (AEs), drug-related AEs, serious adverse events (SAEs), AEs leading to study drug discontinuation, and serial observations including vital signs, physical examinations, clinical laboratory tests (hematology, chemistry and coagulation, urinalysis, standard urinary parameters, urinary biomarkers), and 12-lead ECGs. Additional safety assessments may be performed if deemed necessary by the Investigator.

Pharmacokinetics

The PK of AVI-7288 will be determined from multiple plasma and urine samples collected over 24 hours following the first administration of study drug on Day 1 and up to 48 hours following the final administration of study drug on Day 14. Trough levels will be measured on Days 2 through 13. The PK parameters to be characterized include but are not limited to the maximum plasma concentration (C_{max}), the apparent volume of distribution at steady state (V_{dss}), the elimination half-life ($t_{½}$), the time at which C_{max} occurs (t_{max}), area under the plasma concentration-curve (AUC), total clearance at steady state (Cl_{ss}), mean residence time (MRT), and renal (i.e., urinary) clearance (Cl_r).

STATISTICAL METHODS:

Safety:

Safety and tolerability of AVI-7288 will be based upon the review of individual values and summary statistics. Incidence of treatment-emergent AEs will be tabulated by counts and percentages. Abnormalities in clinical laboratory, vital signs, and ECG will be based on pre-defined normal ranges and will be tabulated by dose group showing subject counts and percentages. Placebo-treated subjects will be pooled across all dose groups.

Pharmacokinetics:

Pharmacokinetic parameters will be summarized by mean, standard deviation (SD), coefficient of variation (CV), and minimum, and maximum for each dose level. Dose proportionality for C_{max} and AUC(s) will be assessed visually by plotting these parameters against dose. Accumulation ratios for C_{max} and AUC(s) and time to steady state will be assessed. The terminal phase following 14 days of consecutive dosing will also be compared to that following single dose (Day 1 profile).

2 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3 ABBREVIATIONS

Abbreviation or Term	Definition
λ_z	elimination rate constant
Acc Ratio	accumulation for C_{max} and AUC
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BQL	below quantitation limit
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
$C_{avg,ss}$	average plasma concentration at steady-state
CL_{ss}	total clearance of drug at steady state
C_{max}	maximum plasma concentration
C_{trough}	trough plasma concentration before dosing
CV	coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
eDCR	electronic data clarification request
FDA	United States Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus

Abbreviation or Term	Definition
HRPO	Human Research Protection Office
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug application
IRB	Institutional Review Board
IV	intravenous
KIM-1	kidney injury molecule-1
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHF	Marburg hemorrhagic fever
mRNA	messenger RNA
MTD	maximum tolerated dose
MRT	mean residence time
NCS	not clinically significant
NOAEL	no-observed-adverse-effect level
NP	nucleoprotein
NSS	normal saline solution
ORP	Office of Research Protections
PHI	protected health information
PK	pharmacokinetic(s)
PMO	phosphorodiamidate morpholino oligomer
PMO*plus*™	phosphorodiamidate morpholino oligomer with positive charges
PT	prothrombin time
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
$t_{½}$	elimination half-life
t_{max}	time at which C_{max} occurs
UACR	urine albumin-to-creatinine ratio

Abbreviation or Term	Definition
USAMRMC	US Army Medical Research and Materiel Command
V_{dss}	apparent volume of distribution at steady state
VP24	viral protein 24
VP40	viral protein 40
WBC	white blood cell

4 INTRODUCTION

Purpose of Study

The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of 14 once daily intravenous (IV) infusions of AVI-7288, a potential post-exposure prophylactic treatment for Marburg hemorrhagic fever (MHF), compared to placebo. Four dose levels of AVI-7288 will be examined: 3, 6, 9, and 15 mg/kg.

Marburg Hemorrhagic Fever

Marburg hemorrhagic fever is a rare human disease caused by Marburg virus, a filamentous, single-stranded, negative-sense RNA virus of the family *Filoviridae*. It was first identified as the cause of a disease outbreak in Marburg, Germany in 1967, when several laboratory workers acquired the infection while processing organs from African green monkeys that had been imported from Uganda. Since then, the vast majority of human infection has occurred in the context of outbreaks within central and southern Africa; the few cases occurring outside of Africa have involved travel to or contact with that continent (Center for Disease Control [CDC] 2010). There is only a single species of Marburg virus, Lake Victoria, of which there are 2 distinct lineages differing in amino acid sequence by approximately 22% (Knipe 2007).

Marburg virus infection is associated with a very high mortality rate. It may be transmitted to the host by way of exposure of mucosal surfaces or abraded skin to infected body fluids or through parenteral inoculation; the contribution of aerogenic transmission in the setting of natural epidemics is unknown. Death rates in the more sizeable MHF outbreaks have ranged from 23% to 88%, and of the 446 cases of MHF reported to date, 82.5% have been fatal (CDC 2010). Because it is highly lethal and readily transmitted from person to person, Marburg virus has been classified by the US CDC as a potential "Category A" agent of bioterrorism, and deemed of high priority.

Clinically, filovirus infections such as Marburg virus are characterized by the acute onset of illness after a typical incubation period of 4 to 10 days, with symptoms initially consisting of fever, chills, myalgia, and malaise. Disease features may evolve to encompass anorexia, nausea, vomiting, abdominal pain, diarrhea, respiratory complaints, conjunctival infection, hypotension, edema, prostration, confusion, and coma. Hemorrhagic manifestations, coagulopathy, maculopapular rash, cytopenias, and increased transaminase levels may also be observed. In nonfatal cases, improvement typically commences at about 7 to 11 days; however, convalescence

is protracted among survivors and may be associated with a number of complications, including myelitis, hepatitis, orchitis, and uveitis (Fauci 2008).

Currently there is no vaccine or established effective therapy for Marburg virus or any other filovirus infection (Mandell 2009). Various experimental interventions including fusion inhibitors, transcription/replication inhibitors, maturation inhibitors, small interfering RNA, antibody therapy, inflammatory modifiers, and coagulation modulators have been preliminarily evaluated, but, in general, in vivo benefits have not been documented. Thus, there is a clear medical need for effective therapy and prophylaxis of Marburg virus infection.

AVI-7288

AVI-7288 is a phosphorodiamidate morpholino oligomer (PMO) capable of bearing positive charges (PMO*plus*™) that targets the viral messenger RNA (mRNA) encoding the Marburg virus nucleoprotein (NP), which is the major nucleoprotein involved in RNA encapsidation. The resultant nucleocapsid is thought to interact with membrane-associated viral protein 40 (VP40) in the viral budding and cellular extrusion process.

AVI-7288 consists of 23 bases and contains 6 positive piperazinyl moieties. Its chemical name is:

> RNA, (P-deoxy) (2',3'-dideoxy-2',3'-imino-2',3'-seco) (2'a-5') (**G**-P-(dimethylamino)-**A** - P-(dimethylamino)-**A** – P-(dimethylamino)– **m^{5}U** - P-(dimethylamino)-**A** - P-(dimethylamino)– **m^{5}U** - P-(dimethylamino)– **m^{5}U** - P-(dimethylamino)-**A** - P-(dimethylamino)-**A** - P-(dimethylamino)–**C** - P-(1-piperazinyl)–**A** - P-(dimethylamino)-**I** - P-(1-piperazinyl)–**A** - P-(dimethylamino)–**C** - P-(1-piperazinyl)– **m^{5}U** - P-(dimethylamino)–**G** - P-(dimethylamino)–**A** - P-(dimethylamino)–**C**- P-(1-piperazinyl)–**A** - P-(1-piperazinyl)–**A** - P-(dimethylamino)–**G** - P-(dimethylamino)– **m^{5}U** -P - (dimethylamino)–C), 5'-[P-[4-[[2-[2-(2-hydroxyethoxy)ethoxy] ethoxy]carbonyl]-1-piperazinyl]-N,N-dimethylphosponamidate.

To date, AVI-7288 has been evaluated in clinical and nonclinical studies as a component of AVI-6003, which entails the sequential administration of AVI-7288 and AVI-7287, a similar PMO*plus* that targets Marburg virus viral protein 24 (VP24). This is because initial nonclinical studies in mouse and guinea pig lethal challenge models suggested that AVI-6003 was the best candidate for post-exposure prophylaxis of Marburg virus. However, subsequent studies in a cynomolgus macaque Marburg virus lethal challenge model demonstrated that AVI-7288 is the only active component in AVI-6003. Therefore, AVI BioPharma amended the Investigational New Drug Application (IND) to remove AVI-7287 from the development plan and to focus on AVI-7288 as a single oligomer candidate for development.

AVI-7288 is being developed as an immediate post-exposure prophylaxis to be administered following documented or suspected exposure to Marburg virus. In general, the development plan will seek to identify and confirm an effective and well-tolerated dose in an appropriate animal challenge model and will attempt to replicate systemic exposures in healthy human volunteers that are comparable to those that afford protection in the experimental model.

Nonclinical Experience with AVI-7288

Support for the efficacy of AVI-7288 derives from studies in mouse, guinea pig, and nonhuman primate lethal challenge models performed at the United States Army Medical Research Institute for Infectious Diseases. In these studies, treatment with AVI-7288 or AVI-6003 (which consists of sequential injections/infusions of AVI-7287 and AVI-7288 in a 1:1 ratio) significantly increased survival in mice, guinea pigs, and nonhuman primates exposed to Marburg virus. As the mouse and guinea pig studies utilized a species-adapted strain of Marburg virus, and as the nonhuman primate model of Marburg virus most closely mimics the course of the disease in humans, the most relevant information for human efficacy derives from nonhuman primate studies.

In the 5 such studies conducted to date, a total of 61 cynomolgus macaques were challenged with lethal viral inoculums (approximately 1000 pfu/monkey) of Marburg virus followed by up to 15 daily doses of AVI-7288 (alone or as part of AVI-6003) (n=58) or placebo or scramble control (n=13). At 28 or 40 days post-infection, 48 of the 58 (82.7%) animals treated with AVI-7288 (alone or as part of AVI-6003) had survived versus none of the placebo-treated animals. The efficacy of AVI-7288 appeared dose dependent: survival rates in animals treated with 3.75 or 7.5 mg/kg of AVI-7288 (administered by IV bolus as part of AVI-6003 doses totaling 7.5 or 15 mg/kg, respectively) showed 60% survival rates, whereas animals treated with 15 mg/kg AVI-7288 (administered by IV bolus alone or as part of a 30 mg/kg dose of AVI-6003) showed survival rates of 92%. As the 15 mg/kg dose of AVI-7288 was the most effective dose tested, it is currently considered the target dose for use in humans.

AVI-6003 was generally well tolerated in 2 separate 28-day, repeat-dose toxicology studies conducted in rat (at doses of 8 to 400 mg/kg/day) and cynomolgus monkeys (4 to 200 mg/kg/day). In both studies, the kidney was identified as the most sensitive organ, with the rat appearing to be the more sensitive species. There were no clear test article-related findings for ophthalmoscopic examinations, hematology or coagulation evaluations, or organ weight evaluations in either species; however, dose-dependent effects on the kidney including proximal tubular degeneration/necrosis and basophilic granules in tubular cells were observed in both. Of

note, the kidney findings were partially recovered by 14 days post last dose in the rat and 30 days post last dose in the monkey, suggesting reversibility. In a subsequent study in which rats administered 15 daily doses of 1.5, 3, 15, or 30 mg/kg AVI-6003 were necropsied at 16 days or 1, 3 or 6 months post last dose, adverse kidney effects (minimal to mild tubular degeneration/necrosis) observed in the 2 highest dose levels were reversible at the 1-month recovery period, while incidental kidney findings (basophilic granules in the proximal tubular cells) observed at all dose levels were completely reversible at the 6-month recovery period. These findings indicate that AVI-6003's effects on the kidney, which most likely reflect accumulation of drug as part of the elimination process, are completely reversible following cessation of treatment.

Further details regarding nonclinical experience with AVI-6003 and AVI-7288 are provided in the Investigator's Brochure.

Clinical Experience with AVI-7288

To date, only 1 clinical study has been conducted with AVI-6003, and none have been conducted with AVI-7288 alone. Protocol 6003-us-101, a first-in-human, double-blind, placebo-controlled, single ascending dose study of AVI-6003, was completed in November 2011. A total of 30 subjects, 6 males and 14 females ranging in age from 18 to 49 years, were randomized to 1 of 6 dose escalation cohorts (0.01, 0.1, 1, 3, 6 and 9 mg/kg) of 5 subjects each. Subjects in each cohort received a single IV infusion of AVI-6003 or matching placebo in a 4:1 ratio and were followed for 28 days. The dose of AVI-7288 consisted of one-half the total dose of AVI-6003 for each cohort (e.g., 0.005, .0.05, 0.5, 1.5, 3, and 4.5 mg/kg).

AVI-6003 was safe and well tolerated at all doses studied. All subjects completed the 28-day study except for 1 who was randomized to the 0.1 mg/kg cohort, had a history of schizophrenia, and withdrew consent following an exacerbation of this illness (assessed as an SAE). Approximately half (54.2%) of the AVI-6003-treated subjects experienced a total of 27 treatment-emergent adverse events (TEAEs), of which only 6 (20.8%) were assessed as related to study treatment. All treatment-related TEAEs were mild in severity and, except for headache, which was reported by 2 subjects, none was reported by more than 1 subject. There were no SAEs other than exacerbation of schizophrenia in the 1 subject noted above, nor were there any discontinuations due study treatment or deaths. There were no clinically significant or dose-dependent effects of AVI-6003 on any of the safety endpoints including clinical laboratory assessments (hematology, coagulation, chemistry, urinalysis, reticulocyte counts, and complement levels), vital signs, electrocardiograms (ECGs), physical examinations, pulse

oximetry, and cardiac telemetry, nor were any gross abnormalities in fluid status, nephrotoxicity, changes in renal function, or changes in biomarkers of renal dysfunction observed.

Pharmacokinetic analyses of both components of AVI-6003 (i.e., AVI-7287 and AVI-7288) indicated that plasma profiles at the higher dose levels plateaued at the last 3 to 4 time points. For AVI-7287, C_{max} at the lowest and highest doses of 0.01 and 9 mg/kg averaged 34.1 and 23,300 ng/mL, respectively, and for AVI-7288, it averaged 36.4 and 26,900 ng/mL, respectively. Systemic clearance (CL_P) was similar for both components: for AVI-7287, it averaged 93.6 mL/hr/kg at 0.01 mg/kg and 123 mL/hr/kg at 9 mg/kg; and for AVI-7288, it averaged 104 and 136 mL/hr/kg, respectively. V_{ss} was also similar across the two components: for AVI-7287, it averaged 189 mL/hr at 0.01 mg/kg and 537 at 9 mg/kg; and for AVI-7288, it averaged 158 and 569 mL/hr, respectively. Elimination half-life was about 2 to 5 hours for both components.

4.1 Summary of Potential Risks

Foreseeable risks to participants in the present study include those related to study drug and those related to study procedures. As noted above, no drug-related safety issues were identified in the single ascending dose study 6003-us-101, in which healthy subjects received a single dose of AVI-6003 (which included sequential infusions of AVI-7287 and AVI-7288 in a 1:1 fixed-dose ratio) at total doses of up to 9 mg/kg. However, reversible effects of AVI-6003 on kidney have been observed in preclinical studies (refer to Section 4 and the Investigator's Brochure for additional details); therefore heightened renal monitoring is included as part of this study.

Foreseeable risks associated with venipuncture include bruising, local pain, swelling, scarring at site, vasovagal syncope, and infection. Measures taken to minimize these risks include performance by trained medical personnel using aseptic techniques. Potential risks associated with ECG include skin irritation. Additional risks associated with laboratory analyses and ECGs include discovery of a previously undetected, significant abnormality. If any significant abnormality is discovered, the subject will be notified and follow-up care with a primary physician or health care provider will be recommended.

Although not observed in animal studies or the single ascending dose study, subjects could experience systemic allergic reactions including symptoms such as rash, fever, chills, difficulty breathing, swelling of the face, lips or tongue, seizure or loss of consciousness. Subjects could also experience local reactions to IV administration, including redness, pain, itching, burning, or sensitivity reactions (headache, fever, nausea, welts) due to use of heparin post-dose to flush the line. To mitigate such risks, subjects will be monitored closely in an in-patient unit during the

14-day dosing period and for 48 hours after completion of the last dose of study drug. Medical emergency equipment will be available at the clinic.

Additional measures to minimize risk to participants include review of clinical safety and laboratory results by an independent Data Safety Monitoring Board (DSMB) on an ad hoc basis and prior to dose escalation as well as pre-specified stopping rules, as detailed in Section 8.2.3.

4.2 Summary of Potential Benefits

This trial is designed to characterize the safety and PK of multiple IV doses of AVI-7288 in healthy human volunteers. Subjects enrolled in the trial are not expected to receive any medical benefit from their participation.

5 STUDY OBJECTIVES

- To evaluate the safety and tolerability of 14 once daily IV infusions of ascending doses of AVI-7288 compared to placebo in healthy male and female subjects
- To evaluate the PK of 14 once daily doses of AVI-7288 in healthy male and female subjects

6 INVESTIGATIONAL PLAN

6.1 Endpoints

6.1.1 Efficacy Endpoints

Efficacy will not be assessed in this Phase 1 study.

6.1.2 Safety Endpoints

The safety and tolerability of AVI-7288 will be assessed through a review and evaluation of:

- The frequency and severity of AEs, SAEs, and discontinuations due to AEs
- Laboratory testing including hematology, coagulation, chemistry, urinalysis, standard urinary parameters, and urinary biomarkers
- Cardiac function as measured by 12-lead ECG
- Vital signs
- Physical examinations

6.1.3 Pharmacokinetic Endpoints

Pharmacokinetic parameters to be estimated from plasma concentration-time data, using actual sampling times, include:

C_{max}	observed maximum plasma concentration (ng/mL)
T_{max}	time to reach the observed maximum plasma concentration (h)
$AUC\tau$	area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (24 hours) (ng.h/mL)
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration C_{last} (ng.h/mL)
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinite time, calculated according to the following equation $AUC = AUC_{last} + C_{last} / \lambda_z$ (ng.h/mL) AUC_{∞} will be reported if $t_{1/2,\lambda}$ is calculable and if C_{last} / λ_z represented 30% or less of the AUC value. AUC values where C_{last} / λ_z is less than 30% but equal to or greater than 20 % of the AUC value will be flagged in the report.
MRT_{∞}	mean residence time, calculated as $AUMC_{\infty}/AUC_{\infty}$
AUC_N	area under the plasma concentration versus time curve ($AUC\tau$ or AUC_{∞}) normalized by the dose
$\%AUC_{\infty,ex}$	percentage of AUC_{∞} obtained by extrapolation, calculated by the following equation:

$$\frac{AUC_{\infty} - AUC_{last}}{AUC_{\infty}} * 100$$

$t_{1/2,\lambda}$	elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$
λ_z	first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve
$C_{max,ss}$	maximum plasma concentration during a dosing interval at steady state
C_{trough}	trough plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose
Swing (%)	$[(C_{max}-C_{min})/C_{min}]*100$
$C_{avg,ss}$	average plasma concentration at steady-state, calculated as $AUC\tau/\tau$
CL_{ss}	total clearance of drug at steady state
V_{dss}	apparent volume of distribution at steady-state, calculated as $MRT_{\infty}*CL_{ss}$
Acc Ratio	accumulation for C_{max} and AUC estimated by dividing the PK parameter on Day 14 by the same parameter on Day 1

In addition, the following PK parameters will be calculated from the urine levels of AVI-7288 treated subjects:

- Amount excreted for each defined urine collection time point
- Cumulative amount excreted over time (up to 1 day after last administration)
- Cumulative percentage of injected AVI-7288 excreted in the urine
- Calculated Cl_r (i.e., urinary clearance).

6.2 Study Design

This is a Phase 1, randomized, double blind, placebo-controlled, multiple-dose, dose-escalation study to assess the safety, tolerability, and PK of AVI-7288 in healthy adult volunteers.

Up to 32 subjects will be randomized to 4 cohorts of 8 subjects each. Within each cohort, 6 subjects will receive AVI-7288 and 2 will receive placebo once daily for 14 days. Every effort will be made to include a similar number of male and female subjects in each cohort. The dose of AVI-7288 will be escalated in each sequential cohort as follows: 3 mg/kg, 6 mg/kg, 9 mg/kg, and 15 mg/kg. Cumulative safety data through Day 21 for each cohort will be reviewed by an independent DSMB prior to dosing of the next dose cohort.

All subjects will be confined to the study center from 1 day prior to the first dose of blinded study drug (AVI-7288 or placebo) until 48 hours after the last dose, i.e., from Days -1 through 16. Subjects will return to the study center for safety evaluations 5 and 26 days post-discharge (i.e., on Days 21 and 42, respectively).

6.2.1 Completion of a Subject's Participation in the Study and Overall Study Completion

Including a screening period of up to 21 days, 1 day to check in to the study unit, 14 days of dosing, and 28 days of safety follow-up post last dose, the study duration for each patient is expected to be approximately 64 days. As previously noted, subjects will be confined to a study unit for 17 of these days.

6.2.1.1 Completion of a Subject's Participation in the Study

The length of a subject's participation will be from the time the informed consent form is signed until completion of the Day 42 assessments. A subject will be considered "completed" when the subject has completed the Day 42 assessments.

6.2.1.1.1 Premature Subject Discontinuation from the Study

Subjects are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further treatment or penalty or loss of benefits to which the volunteer is otherwise entitled. A subject's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor.

Subjects who receive at least 1 dose of investigational product and who are withdrawn from the study during the 14-day dosing period will be encouraged to remain in the study unit for 48 hours after their last dose of study drug to collect the discharge evaluations (same as Day 16 evaluations) and to return for the Day 21 and Day 42 outpatient visits. Subjects who are withdrawn from the study after the 14-day dosing period will be asked to complete all early termination assessments (same as Day 42 assessments) as soon as possible. Moreover, every reasonable effort should be made to determine the reason for a subject's decision to withdraw from the study and the importance of continuing safety follow-up through Day 42 should be stressed. If applicable, at least 3 attempts should be made to contact the subject either by telephone, electronic mail, or registered mail.

Post-study SAEs will be reported according to Section 10.3.4.

At the end of the subject's participation in the study, the Investigator will document the reason(s) for study discontinuation on the appropriate screen/form of the electronic case report form (eCRF). As specified in Section 8.4, subjects who are withdrawn from the study after receiving their first dose of study drug will not be replaced.

6.2.1.2 Overall Study Completion

The study will be considered to be complete when the last subject has completed their Day 42 or is withdrawn from the study.

6.3 Discussion of Study Design

This study will assess the safety and tolerability and the basic PK profile of repeat doses of AVI-7288 in healthy adult volunteers. In particular, the renal safety of AVI-7288 will be closely evaluated with both standard and exploratory biomarkers of renal function. Pharmacokinetic data from this and any ensuing human study will be critical for confirming that a selected dose produces exposures in humans comparable to those shown to be effective in nonhuman primate lethal challenge studies, and thus would be reasonably likely to confer protection from lethal infection in humans.

A staggered dosing scheme, which allows escalation of dose to the next dose level only if no significant safety concerns are identified in the prior dose cohort, has been adopted to mitigate potential risk to the subjects. During regular evaluations of clinical, laboratory, and AE data, the DSMB may identify a potential safety signal for AVI-7288 that could lead to study termination or other changes in the protocol including lowering or repeating a dose level. Overall, these safeguards provide a strategy that will minimize any safety concerns associated with this experimental study drug.

Randomization will be used to avoid bias in the assignment of subjects to AVI-7288 or placebo, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across the assigned treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Blinded treatment (AVI-7288 versus placebo) will be used to reduce potential bias during data collection and evaluation of clinical (safety) parameters.

7 SUBJECT POPULATION AND SELECTION

The study population for this Phase 1 multiple ascending dose study consists of healthy male and female subjects aged 18 to 50 years, inclusive, with a body mass index (BMI) of 18 to 35 kg/m^2, inclusive.

7.1 Inclusion Criteria

A subject must meet all of the following criteria to be eligible for this study.

1. Man or woman 18 to 50 years of age, inclusive, at the time of screening.
2. Body mass index 18 kg/m^2 to 35 kg/m^2, inclusive, at the time of screening and Check-in (Day -1).
3. Good general health (no chronic health conditions) as determined by the Investigator.
4. Female subjects must be of non-childbearing potential or must, in conjunction with their sexual partner(s), use 2 forms of medically acceptable contraception (e.g., oral contraception in conjunction with a male condom) during the screening period and for the entire duration of the study including the 28-day post last dose follow-up.
5. Male subjects must either be sterile or agree to use, for the entire duration of the study including the 28 day post last dose follow-up, a male condom and the female sexual partner must also use a medically acceptable form of birth control (e.g. oral contraceptives).
6. Able to understand the requirements of the study, to provide written informed consent (as evidenced by signature on an informed consent document that is approved by an Institutional Review Board (IRB), and agreeable to abiding by the study restrictions.

7.2 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from this study.

1. Pregnancy or breastfeeding.
2. A positive urine or blood screen for drugs of abuse, including alcohol.
3. Use of any tobacco- or nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to Check-in (Day -1).

4. A positive cotinine test indicating recent nicotine use.
5. Donated blood within 90 days or plasma within 30 days of first dose on Day 1.Active substance abuse or any medical or psychiatric condition that could jeopardize the subject's safety or the subject's ability to comply with the protocol.
6. Use of any medications apart from vitamins, acetaminophen, or hormonal contraception within 14 days of first dose on Day 1. Subjects with mild seasonal allergies may use antihistamines at the discretion of the Investigator after approval by the Sponsor Medical Monitor.
7. Participation in any interventional clinical trial within 45 days of first dose on Day 1 (i.e., received any other investigational drug).
8. Recipient of an organ transplant (solid or hematopoietic).
9. Prolonged QTcF interval >440 ms for males or >460 ms for females using the average of the triplicate ECGs collected during screening, on Day -1, or just prior to dosing on Day 1.
10. Other clinically significant ECG abnormality, as determined by the Investigator.
11. Any clinically significant abnormal hematology, chemistry, coagulation, or urinalysis value, as determined by the Investigator.
12. Glomerular filtration rate (GFR) of <80 mL/min, based on the Modification of Diet in Renal Disease equation.
13. Urine-albumin-to-creatinine ratio (UACR) >30 mg/g.
14. Positive test for human immunodeficiency virus (HIV-1 serology) or known HIV infection.
15. Positive result for hepatitis B surface antigen (HBsAg) or for hepatitis C virus (HCV) antibody.
16. Use of alcohol-containing foods or beverages within 72 hours prior to Check-in on Day -1.
17. Use of caffeine-containing foods or beverages within 24 hours prior to Check-in on Day -1.

18. Febrile illness or significant infection within 48 hours before administration of the first dose of study drug on Day 1.

Note: Inclusion of each subject will be reviewed with a member of AVI BioPharma Clinical Personnel prior to enrollment in the trial. Written approval from a member of AVI BioPharma Clinical Personnel is required prior to randomization.

8 TREATMENTS

8.1 Treatments Administered

8.1.1 Test Article

Active drug consists of AVI-7288 formulated with phosphate buffered saline at a concentration of 50 mg/mL. AVI-7288 is supplied in aseptically filled, 5 mL vials containing 5 mL AVI-7288.

8.1.2 Reference Treatment

A 150 mL NSS infusion bag will be labeled appropriately and used for the placebo control.

8.1.3 Packaging and Labeling

The label text for AVI-7288 will comply with Good Manufacturing Practice (GMP) and other applicable regulatory requirements and will minimally include the protocol number ("AVI-us-7288"), contents of the vial ("AVI-7288"), the appropriate cautionary statements per 21 CFR 312.6, concentration (50 mg/mL), lot number (or alternative code), storage conditions, and the name of the Sponsor/manufacturer ("AVI BioPharma, Inc.")

8.1.4 Storage

Vials of AVI-7288 will be shipped to the investigational site pharmacy with cold packs. Vials must be stored at a consistent temperature from 2 °C to 8 °C in a secured, limited-access area with temperature recording, controls, and monitoring. Placebo (NSS) will be maintained per the manufacturer's specifications.

8.1.5 Preparation and Administration of the Investigational Product

AVI-7288 and placebo (NSS) will be prepared by qualified study staff who do not otherwise participate in collection of study data or have direct contact with participating subjects. Blinded, qualified study staff will administer study drug as an IV infusion over 30 minutes using an infusion pump; study drug will be administered at approximately the same time each day for 14 days.

AVI-7288

The dose of AVI-7288 for each dose cohort is noted in Table 8-1 below. The dose of AVI-7288 will be calculated based on the subject's dose cohort and weight, and the appropriate volume will be drawn into a syringe. The same volume will then be removed from a 150mL bag of NSS and the syringe of AVI-7288 will be injected into the bag of NSS. The bag will then be labeled with the subject's treatment number, and date and time of study drug preparation.

Table 8-1: Study Drug Dosing Regimen by Cohort

Cohort	Dosing Regimen
1	AVI-7288 at 3 mg/kg (or placebo) IV q day x 14 days
2	AVI-7288 at 6 mg/kg (or placebo) IV q day x 14 days
3	AVI-7288 at 9 mg/kg (or placebo) IV q day x 14 days
4	AVI-7288 at 15 mg/kg (or placebo) IV q day x 14 days

Placebo

Placebo control consists of approximately 150 mL NSS; the IV bag will be labeled with the subject's treatment number, and date and time of preparation.

8.2 Dosing Considerations

8.2.1 Dose Selection Rationale

The present study will examine the safety and tolerability of 14 once daily IV infusions of 3, 6, 9 or 15 mg/kg AVI-7288, administered in sequential dose cohorts. Pharmacokinetic findings from this study will be compared to the PK of AVI-7288 when administered to nonhuman primates infected with Marburg virus to determine the appropriate scaling required to produce human exposures comparable to those seen in protected animals.

This trial is the first in man study of AVI-7288 alone; however, AVI-7288 was previously administered to human volunteers in combination with AVI-7287 in the ascending single-dose study of AVI-6003, 6003-us-101. In that study, single IV infusions of AVI-6003 (which is a 1:1 combination of AVI-7287 and AVI-7288) were safe and well tolerated at doses ranging from 0.01 to 9.0 mg/kg, and no clinically significant changes in any of the plasma or urinary kidney biomarkers were observed. At a minimum, these findings suggest that AVI-7288 alone will be safe and well tolerated in humans at doses up to 4.5 mg/kg. The average AUC_{0-24} for the plasma concentrations of AVI-7288 in study 6003-us-101 were 23,000 ng.mL/hr for the 3 mg/kg dose of AVI-7288 and 32,000 ng.mL/hr for the 4.5 mg/kg dose of AVI-7288.

Nonclinical studies of AVI-6003 further support the safety of AVI-7288 for human use; 28 daily doses of AVI-6003 were tolerated in nonhuman primates at doses up to and including 200 mg/kg/day and in rats at doses up to 400 mg/kg. Recently, we conducted a rat study in which the potential reversibility of kidney findings observed in prior animal studies of AVI-6003 (tubular degeneration/necrosis) was investigated. Rats given 1.5, 3.0, 15.0, or 30.0 mg/kg AVI-6003

once a day for 15 days were necropsied at 16 days or 1, 3 or 6 months post last dose. While degeneration in the proximal tubules of the kidney was seen at doses of 15 or 30 mg/kg immediately following dosing, all such findings were absent by the 1-month recovery period, and all histological findings in the kidney were absent by 6 months post-dosing. Based on these findings, the no-observed-adverse-effect level (NOAEL) during the recovery phase was considered to be the highest dose tested of 30 mg/kg/day of AVI-6003. At that dose of AVI-6003, the average exposure to the AVI-7288 component of AVI-6003 was approximately 20,000 ng.mL/hr following the first day of dosing. Together, the preclinical and human safety data suggest that once daily dosing in humans with 3.0 mg/kg will be well tolerated and is therefore a justifiable starting dose for this 14-day human study.

As previously mentioned in Section 4, administration of AVI-7288 (alone or in combination with AVI-7287 as part of AVI-6003) once a day for 15 days markedly increased the survival of cynomolgus macaques that had been exposed to lethal viral inoculums of Marburg virus, and the efficacy of AVI-7288 appeared dose dependent. Survival rates in animals treated with 3.75 or 7.5 mg/kg of AVI 7288 (as part of 7.5 or 15 mg/kg doses of AVI-6003) were 60%, whereas animals treated with 15.0 mg/kg AVI-7288 (alone or as part of a 30.0 mg/kg dose of AVI-6003) had a survival rate of 92%.

As AVI-7288 was most effective at the 15 mg/kg dose in cynomolgus monkeys, the exposure achieved in monkeys at this dose level will be established in an upcoming pharmacokinetic/pharmacodynamic study. The doses selected for the current human study are intended to escalate up to and include 15 mg/kg, to test whether exposures equivalent to or greater than that of the efficacious exposure in cynomolgus monkeys can be safely achieved.

Please refer to the Investigator's Brochure for additional information on the clinical and nonclinical studies referred to in this section.

8.2.2 Dose Escalation

An independent DSMB will evaluate the safety of all treated subjects in an ongoing fashion. In addition, the DSMB will convene to review each cohort's cumulative safety data through Day 21 at least once after each cohort has completed dosing in order to make recommendations to the Sponsor concerning the advisability of escalating to the next dose. Additional details regarding the DSMB are included in Section 13.3.

8.2.3 Treatment Interruption or Discontinuation

A subject's study treatment may be discontinued at any time at the subject's request or at the discretion of the Investigator or Sponsor. The following may be justifiable reasons for the Investigator or Sponsor to discontinue a subject from treatment:

- The subject was erroneously included in the study (i.e., was found to not have met the eligibility criteria).
- The subject experiences an intolerable AE.
- The subject is unable to comply with the requirements of the protocol.
- The subject participates in another investigational study without the prior written authorization of the Sponsor.

In addition, dosing of an individual subject will be suspended and the Sponsor will be notified within 24 hours if the subject develops any of the following:

- An SAE, a Grade 4 AE or a Grade 4 laboratory event, for which no clear alternative explanation, other than study drug, exists (grades are according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" as noted in Section 10.2.2).
- A Grade ≥3 rash and/or Grade ≥3 allergic reaction (e.g., generalized urticaria, angioedema).
- A Grade ≥3 local infusion site reaction, including pain, tenderness, erythema or swelling.
- Serum creatinine ≥Grade 2 toxicity (≥1.8 mg/dL).
- A confirmed >3-fold increase from pre-dose on Day 1 in UACR to an absolute value >30 mg/g.

As noted in Section 6.2.1.1.1, subjects who receive at least 1 dose of investigational product and who are withdrawn from treatment during the dosing period (Days 1 through 14) will be encouraged to remain in the study unit for 48 hours after the last dose of study drug to collect the discharge evaluations (same as Day 16 evaluations) and to return for the Day 21 and Day 42 outpatient visits. Subjects who are withdrawn from the study after the 14-day dosing period will be asked to complete all early termination assessments (same as Day 42 assessments) as soon as possible and the importance of continuing safety follow-up through Day 42 should be stressed.

8.2.3.1 Cohort Stopping Rules

The safety of this study will be overseen by an independent DSMB as noted above and outlined in Section 13.3. If safety concerns arise during the course of the planned DSMB reviews, or outside these reviews, dosing may stop until these concerns have been addressed.

In addition, dosing will be interrupted to allow for an ad hoc review of cumulative safety data by the DSMB if any of the following conditions are met within a cohort:

- Two or more subjects develop the same or clinically similar Grade ≥3 AE or laboratory abnormality.
- Two or more subjects develop a serum creatinine ≥Grade 2 toxicity (≥1.8 mg/dL).
- Two or more subjects who are not menstruating females develop a confirmed >3-fold increase from pre-dose on Day 1 in UACR to an absolute value >30 mg/g.

The DSMB will be notified by the Sponsor within 24 hours of the Sponsor learning of the events above. The DSMB will evaluate available safety data and may make one of the following recommendations:

- Resume dosing of the subject(s) or dose cohort at the same dose level, a reduced dose level, or the next dose level.
- Permanently discontinue dosing of the subject(s) or dose cohort.
- Permanently discontinue the study.

Any decision to interrupt, restart, or discontinue the study will be made by the Sponsor in consultation with the DSMB. The outcome will be communicated to the Investigator by the Sponsor. The FDA will be promptly notified of study suspension or discontinuation related to safety concerns. Any suspension or discontinuation of the trial for any reason will also be promptly reported to the IRB and the US Army Medical Department Medical Research and Material Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO).

8.2.3.2 Determination of the Maximum Tolerated Dose

The maximum tolerated dose (MTD) of AVI-7288 will be the dose below the level at which ≥2/6 of subjects on active drug in any specific dose cohort experience any of the following:

- Serum creatinine ≥Grade 3 toxicity (≥2.1 mg/dL).
- Treatment-related AE that is rated as severe.

If ≥3/6 actively treated subjects in a cohort experience the same treatment-related clinically significant AE, then the MTD is considered exceeded and the next cohort may receive the same or a lower dose as judged appropriate by the DSMB in consultation with the Sponsor and the Principal Investigator.

The MTD may be confirmed by enrolling the next cohort at the same dose. If no additional similar study drug-related AEs are observed, then this dose will be considered the MTD.

In order to make these assessments, the blind for the concerned subjects will be broken. Should any concerned subject be receiving placebo, the DSMB, in conjunction with the Sponsor, may decide to continue the dose escalation as scheduled. This decision may be taken after review of all available safety and tolerability data.

8.3 Prior and Concomitant Medications and Therapeutic Procedures

As specified in the exclusion criteria (Section 7.2) the use of following prior medications are prohibited:

- Nicotine patches, nicotine lozenges, or nicotine gum within 6 months prior to Day -1
- Any other medications (apart from vitamins, acetaminophen, or hormonal contraception) within 14 days prior to the administration of study drug on Day 1 (note that subjects with mild seasonal allergies may have used antihistamines at the discretion of the Investigator after approval by the Sponsor Medical Monitor).
- Any other investigational drug within 45 days prior to the study

The following concomitant medications may be used during the study:

- Vitamins
- Acetaminophen
- Hormonal contraception
- Antihistamines

Other concomitant medications may be used only after receiving prior approval from the Sponsor's Medical Monitor. In addition, medications may be used for the treatment of AEs as needed, using a minimalist approach.

8.4 Method of Assigning Subjects to Treatment

Approximately 100 subjects will be screened to allow a maximum of 32 subjects to be dosed with AVI-7288 or placebo (4 dose cohorts, 8 subjects per cohort).

Qualifying subjects will be randomized sequentially in successive cohorts, with each cohort identified by the first digit of the randomly assigned treatment number (e.g., 101 to 108 will denote subjects in the first cohort, 201 to 208 will denote subjects in the second cohort, and so on). A subject who has been enrolled and meets all of the inclusion criteria and none of the exclusion criteria at Screening and after evaluation on Day -1 will be randomized within the current cohort through the allocation of the next sequential treatment number on Day 1.

To facilitate enrollment of each cohort, up to 4 spare subjects may undergo Day -1 assessments simultaneously with those subject(s) designated for dosing on Day 1. These spare subjects will not be randomized unless another subject is disqualified from dosing based on the results of their Day 1 assessments or withdraws from the study after randomization but before initiating dosing. If a spare subject is randomized in place of a subject who is disqualified from dosing based on the results of their Day 1 assessments, then the spare subject should be randomized as described above. If a spare subject is a replacement for a subject who was randomized but did not initiate dosing, the replacement subject will be assigned a treatment number by adding 10 to the treatment number of the subject they are replacing (e.g., the replacement subject is assigned treatment number 111 when replacing the subject who was assigned treatment number 101). The replacement subject will receive the same treatment that was assigned to the subject they are replacing. Once 8 subjects in a given cohort have initiated dosing, no further subjects will be dosed in that cohort. If a spare subject(s) is not needed for replacement, the subject will have the option to undergo Day -1 assessments with the next dosing cohort (if applicable) and if qualified, the subject will be randomized within that cohort.

Subjects who withdraw from the study after initiating dosing will not be replaced.

8.5 Blinding and Randomization

This is a double-blind study, which means that the subject, the Investigator, study personnel, and Sponsor will be blinded to the treatment assignments (except for as noted below).

The randomization code will be generated by an unblinded statistician at the contract research organization. The study drug will be assigned by an unblinded person who is designated and authorized to dispense study drug according to the randomization code. A second individual who is authorized to verify the dose and assignment will also be unblinded to the subject's treatment assignment. Neither of these individuals will have interaction with the subjects, and both will be instructed not to divulge the randomization assignment to others under any circumstances, unless directed to do so by the Investigator in the interests of the subject's safety.

The blinding code of the study drug must be broken only in exceptional circumstances, such as when knowledge of the study drug is essential for treating a subject due to an SAE. If time permits, the site must contact the Sponsor Medical Monitor, who will in turn authorize the unblinding for that subject. If time does not permit, the Investigator may authorize breaking of the blind and then notify the Sponsor Medical Monitor. If a patient's study treatment is revealed, the subject number, time, date, and reason for unblinding must be recorded in the eCRF; the

results of the unblinding (treatment allocation) should not be recorded in the medical record. Study personnel who were unblinded will also be identified.

8.6 Treatment Compliance

Treatment compliance will be assessed via compliance with daily infusions and will be assured by the staff who administer study drug.

9 EFFICACY AND SAFETY ASSESSMENTS

9.1 Study Schedule of Events

A schedule outlining the study assessments and times of assessments is shown in Appendix I: Schedule of Study Events. Written informed consent to participate in this study must be obtained from the subject prior to participation in any study related assessments or procedures.

9.2 Study Visits

This study will consist of a screening period of up to 21 days, 1 day to check in to the study unit, a 14-day treatment period, and a 28-day post last dose safety follow-up period. Eligible subjects will check-in to the clinic on Day -1 and complete additional evaluations to confirm eligibility. Eligible subjects will receive once-daily infusions of blinded study drug, AVI-7288 or placebo, on Days 1 through 14, and will be discharged 48 hours after their last dose, on Day 16, provided all assessments are completed and the subject is evaluated as being stable and in good health. Subjects will return to the clinic on Days 21 and 42 to complete safety follow-up.

9.3 Screening Assessments

The screening assessments specified in Appendix I: Schedule of Study Events will be performed in the following order:

- Sign written Informed Consent.
- Demographics
- Measurement of height and weight
- Complete medical history (including past blood donation history, tobacco use, and history of previous investigational drug/device study participation)
- Prior and concomitant medications (see Sections 8.3 and 9.4.2.1)
- Urine collection for pregnancy test (in females as applicable), urinalysis, urinary parameters, and urinary biomarkers (see Section 9.4.2.5)
- 12-lead ECG (see Section 9.4.2.2)
- Vital sign measurements (see Section 9.4.2.3)
- Complete physical examination (Section 9.4.2.4)
- Drug screen (screen for use of alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and nicotine; urine and/or blood testing may be performed according to the means available to the Phase 1 unit; if urine is used samples will be obtained prior to ECGs)

- Blood collection for pregnancy test or follicle stimulating hormone (FSH) test (in females as applicable), drug and alcohol screen, chemistry, hematology, coagulation, and serology (e.g., Hepatitis B surface antigen, Hepatitis C antibody, and HIV) (see Section 9.4.2.5)

Note that if abnormal results on screening assessments are obtained that disqualify a subject from participation, such as a positive HIV, hepatitis B, or hepatitis C test or any clinically significant (CS) chemistry or hematology result, the subject will be given a copy of the laboratory results and advised to take them to his/her health care provider. If a subject withdraws during the screening period and any significant abnormalities are discovered, every attempt will be made to notify the subject of this fact and encourage the subject to seek appropriate care from his/her primary physician or other health care provider.

9.4 Treatment Period Assessments

9.4.1 Efficacy Assessments

Efficacy data will not be collected during this Phase 1 study.

9.4.2 Safety Assessments

Safety parameters will include the use of concomitant medications, physical examinations, ECGs, vital signs, clinical laboratory testing (e.g., hematology, chemistry, coagulation, urinalysis, and urinary biomarkers), and collection of AEs (from first dose as described in Section 10). Of note, throughout the study, the following assessments will be performed in the following order:

- Urine collection for safety laboratory assessments
- 12-lead ECG (after the subject has been lying still for at least 15 minutes).
- Vital sign measurements (to be obtained immediately after ECG recording)
- Blood collection for safety laboratory assessments
- Blood collection for PK testing (immediately before study treatment administration when applicable). Sample collection for PK testing is described in Section 9.5.

It is necessary to maintain the order of assessments as listed above when more than one assessment is requested at any given time point. When multiple assessments are collected, the PK collection should always be taken as close to the exact time noted as possible, and all other assessments will be collected or performed around that time. The assessment timing will be approximate, but within reason, in relation to the protocol specified time point.

9.4.2.1 Prior and Concomitant Medications and Therapies

Review of all concomitant medications, changes in dosage of concomitant medications, and concomitant therapies will be assessed at each visit from the time the subject has provided signed informed consent.

9.4.2.2 Electrocardiogram

A 12-lead ECG will be obtained at the time points specified in Appendix I: Schedule of Study Events. ECGs will be performed only after the subject is positioned supine, resting, and quiet for a minimum of 15 minutes.

ECGs will be performed in triplicate, with at least 1 minute between each ECG, during Screening, on Day -1 and prior to dosing on Day 1; all other ECGs will be performed a single time.

ECGs will be sent to a central ECG lab and reviewed and interpreted by a cardiologist. The interpretation of the report will be documented and sent to the site. The Investigator will receive and review the results of the ECG report and designate the findings as normal or abnormal (CS or not clinically significant [NCS]).

9.4.2.3 Vital Signs

Vital signs (oral temperature, pulse, respiratory rate, and blood pressure) will be measured after subjects have remained seated for at least 5 minutes at the time points specified in Appendix I: Schedule of Study Events. Pulse and respiratory rate will be measured over 1 minute; oral temperature will be recorded in degrees Celsius (°C**)**.

On Dosing Days 1 through 14, vital signs will be collected prior to dosing and again approximately 1 hour post dosing.

Clinically significant changes from just prior to dosing will be documented in the subject source records and eCRF as an AE.

9.4.2.4 Physical Examination

Complete physical examinations will be conducted at the time points specified in Appendix I: Schedule of Study Events. Physical examinations will be performed by the Investigator, an MD Sub-Investigator, or a Nurse Practitioner (if licensed in the state to perform physical examinations), and will include assessment of general appearance; skin; lymph nodes; head, eyes, ears, nose, and throat (HEENT); chest/lungs; abdomen, and the cardiovascular,

musculoskeletal, and neurological systems. Clinically significant changes from just prior to first dose will be documented in the subject source records and eCRF as an AE.

In addition, focused physical examinations may be performed throughout the study on an as-needed basis, e.g., when assessing symptoms of an AE.

9.4.2.5 Clinical Laboratory Tests

The following clinical laboratory tests will be collected at the time points specified in Appendix I: Schedule of Study Events and analyzed by an accredited laboratory selected by the Sponsor (see Appendix V: Additional Study Information):

Urinalysis[1]:	Bilirubin, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, microscopy, urine microscopy including red blood cells, white blood cells, bacteria, yeast, epithelial cells and other abnormalities such as casts, crystals and renal tubular epithelial cells
Urinary parameters[1]:	Quantitative albumin, total protein, creatinine
Urinary biomarkers[1]:	Kidney injury molecule-1 (KIM-1), cystatin C, and β2-microglobulin, each normalized to urine creatinine
Hematology:	Red blood cells (RBCs), total white blood cells (WBCs), hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and abnormal cells (if applicable)
Coagulation:	Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
Full Chemistry:	Sodium, chloride, potassium, calcium, glucose, creatinine, blood urea nitrogen (BUN), albumin, uric acid, total bilirubin, alkaline phosphatase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), lactase dehydrogenase (LDH), total protein, and cholesterol
Limited Chemistry:	BUN and creatinine

[1]Use first morning urine on days when subject is confined to the unit.

Any value outside of the current reference ranges for the laboratory performing the test will be flagged on the laboratory results. The Investigator will score all abnormal assessment results as

either clinically significant (CS) or not clinically significant (NCS). Clinical significance is defined as any variation in assessment results that has medical relevance resulting in an alteration in medical care. If clinically significant deterioration from baseline (defined as the last value collected prior to dosing) levels is noted, the changes will be documented in the eCRF as an AE, according to Section 10.4. The Investigator will continue to monitor the subject with additional assessments until:

- Values have reached normal range and/or baseline levels; or
- In the judgment of the Investigator together with the Sponsor Medical Monitor, abnormal values are not related to the administration of test article or other protocol-specific procedures, and additional assessments are not medically indicated.

9.5 Pharmacokinetic Assessments

Blood and urine samples for PK analysis will be collected at the time points specified in Appendix I: Schedule of Study Events and indicated below:

On Day 1:

- Plasma for PK sampling will be collected immediately pre-dose, at approximately 10 and 30 minutes post-dose, and at approximately 1, 1.5, 2, 4, 6, 8,12, 16, and 24 hours post-dose (collection of plasma 24-hours post dose will also serve as the trough sample for Day 2)
- Urine for PK sampling will be collected at approximately 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours post-dose. Subjects will be asked to void within 30 minutes before dosing to empty bladder pre-dose, and then approximately 4, 8, 12 and 24 hours post-dose to complete the preceding urine collection interval.

On Day 14

- Plasma for PK sampling will be collected immediately pre-dose, at approximately 10 and 30 minutes post-dose, and at approximately 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 28, 32, 36, and 48 hours post-dose (collection of plasma pre-dose on Day 14 will also serve as the trough sample for that day)
- Urine for PK sampling will be collected at approximately 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours post-dose. Subjects will be asked to void within 30 minutes before dosing to

empty bladder pre-dose, and then approximately 4, 8, 12, and 24 hours post-dose to complete the preceding urine collection interval

Plasma for PK sampling will also be collected immediately prior to dosing each day for determination of trough values.

10 ADVERSE EVENT REPORTING

Subjects will be evaluated for new AEs and the status of existing AEs on an ongoing basis as indicated in Appendix I: Schedule of Study Events. The Investigator may elicit symptoms using an open-ended question, followed by appropriate questions that clarify the subject's verbatim description of AEs or change in concomitant medications. All AEs from initiation of first dose through Day 42 (+/-2) will be recorded in the subjects' source documentation and then in the eCRF. As noted in Section 10.3.1, adverse events occurring after signed informed consent has been obtained and prior to initiation of dosing will be recorded as medical history.

10.1 Definitions

10.1.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject, which does not necessarily have a causal relationship with the investigational product (active or placebo drug, biologic, or device). An AE can therefore be any unfavorable and unintended symptom, sign, disease or condition, or test abnormality whether or not considered related to the investigational product.

Adverse events include:

- Symptoms described by the subject or signs observed by the Investigator or medical staff.
- Test abnormalities (laboratory tests, ECG, etc.) that result in an alteration in medical care (diagnostic or therapeutic).

Abnormalities present at baseline are considered AEs only if they reoccur after resolution or they worsen during the study.

10.1.1.1 Unexpected Adverse Events

In this study, an unexpected adverse event is one which:

- Is not previously reported as associated with AVI-7288 (or AVI-6003), as referenced in the Investigator's Brochure.
- May be symptomatically and pathophysiologically related to an AE listed in the Investigator's Brochure, but differs from the event because of greater severity or specificity.

Food and Drug Administration (FDA)-reportable AEs are AEs that are associated with the use of the drug and are serious and unexpected.

10.1.2 Definition of a Serious Adverse Event

An SAE is any AE that results in any of the following:

Death: The subject died as the result of the event.

Life-threatening event: Any AE that places the subject, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that, had it occurred in a more severe form, might have caused death.

Required or prolonged inpatient hospitalization: The AE resulted in an initial inpatient hospitalization or prolonged an existing hospitalization of the patient/subject. If a patient/subject is hospitalized as part of the clinical use of the product, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.

Persistent or significant disability/incapacity: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.

Congenital anomaly/birth defect: A congenital anomaly/birth defect that occurs in the offspring of a subject exposed to the investigational product.

Important medical events: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.2 Evaluation of Adverse Events/Serious Adverse Events

10.2.1 Relationship to Study Treatment

Assessment of the association between the AE and study exposure is important for regulatory reporting. For each AE/SAE, the Investigator determines whether there is a reasonable possibility that the AE may have been caused by the study treatment according to the categories below:

Unrelated: The event is clearly not related to study drug.

Possibly: The event could be related to study drug.

Probably Related: The event is likely related to study drug.

Definitely Related: The event is clearly related to study drug.

In judging relationship to investigational product, it is expected that the temporal sequence of onset of the event during or after administration of investigational product and the existence of other potential causes will be taken into account. AEs that the Investigator considers to be possibly, probably, or definitely related to the study drug will be considered to constitute drug-related AEs for the purposes of analysis and regulatory reporting.

A relationship to the investigational product must be given for each AE/SAE recorded, even if there is only limited information at the time. The Investigator may change his/her opinion of causality in light of follow-up information, amending the AE/SAE report accordingly.

10.2.2 Severity Grading of Adverse Event Scoring

Note that severity should not be confused with seriousness, the latter of which is defined in Section 10.1.2, and which serves as a guide for defining regulatory reporting obligations.

The Investigator will determine the severity of an AE using the criteria specified in the FDA's guidance document, "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" (2007). This scale, which will be provided to the Investigator and staff, was selected for this study because it has been developed by the FDA in conjunction with external input, and is specifically designed for assessing AEs in healthy volunteers who receive a prophylactic intervention.

For each AE, the Investigator should record the severity grade attained according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" criteria, where applicable, as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening). If grading criteria do not exist for a specific AE, the Investigator should grade the severity of the AE using the following guidelines:

Grade 1 (Mild):	Awareness of sign or symptom, but easily tolerated; of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation.
Grade 2 (Moderate):	Discomfort or functional impairment sufficient to cause mild interference with usual activities; may require active therapeutic intervention.
Grade 3 (Severe):	Moderate to marked interference with usual activities and/or substantial dysfunction involving one or more organ or body systems; requires therapeutic intervention.

Grade 4 (Life-threatening):	An AE that places the subject's life in immediate jeopardy.
Grade 5 (Fatal):	An AE that is fatal.

10.2.3 Outcome

Outcome describes the status of the AE. The Investigator will provide information regarding the subject outcome of each AE.

10.2.4 Action Taken Regarding the Investigational Product

The Investigator will provide information regarding the action taken with respect to the investigational product in response to the AE.

10.3 Timeframe for Collection of Adverse Events/Serious Adverse Events

10.3.1 Adverse Events Occurring Prior to Study Treatment

Any or AEs or SAEs occurring after informed consent has been obtained and prior to initiation of study drug will be recorded as medical history.

10.3.2 Adverse Events Occurring During and After Study Treatment

Adverse events and SAEs will be collected from initiation of study drug on Day 1 through Day 42 or early termination.

AEs will be collected on an ongoing basis. In addition, on dosing days (Days 1 through 14) the subject should be assessed for AEs immediately prior to and approximately 1 hour after dosing.

10.3.3 Adverse Events Occurring Following Subject Discontinuation of Treatment

For subjects who have received at least 1 dose of study drug and who prematurely discontinue study treatment or the study, AEs will continue to be recorded until at least 30 days after the last dose of study drug where possible. See Section 10.3.4 for reporting requirements after the subject completes the study.

10.3.4 Serious Adverse Events Occurring Following Subject Completion of the Study

If, at any time after the subject has completed participation in the study (as defined in Section 6.2.1.1), the Investigator or study staff becomes aware of an SAE that the Investigator believes is possibly, probably, or definitely related to the investigational product (see

Section 10.2.1), then the event and any known details should be reported promptly to the Sponsor. Reporting of SAEs will be done according to the instructions in Section 10.5.

10.4 Recording of Adverse Events/Serious Adverse Events

All AEs/SAEs experienced by the subject will be recorded in the subject's source documentation and then in the eCRF. Information including a concise description of the event; date and time of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, and relationship to investigational product; and action taken regarding the investigational product will be recorded. Resolution occurs when the subject has returned to his/her baseline state of health or further improvement or worsening of the event is not expected.

Abnormalities in vital signs, laboratory results, and other safety assessments noted in Section 9.4.2 will be recorded as an AE if they meet the definition of an AE (see Section 10.1.1). When possible, a diagnosis should be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to that diagnosis. A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. If the condition is not known, the procedure must be reported as an AE instead. Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE.

All SAEs experienced by the subject will be recorded on an SAE Report Form and reported to the Sponsor according to Section 10.5.

10.5 Reporting of Serious Adverse Events

The necessity and time requirements for reporting of SAEs to the Sponsor or its designee and/or regulatory agencies are as follows:

- All SAEs must be reported to the Sponsor/designee within 1 calendar day of the Investigator's first knowledge of the event by fax or e-mail regardless of relationship to study procedures or treatment. The Investigator is requested to supply detailed information regarding the event at the time of the initial report.
- A completed Clinical Study SAE Report Form containing a detailed written description of the event along with additional supporting documents (e.g., discharge letters, autopsy reports, and other documents) will be faxed to the Sponsor or Sponsor designee within 2 calendar days of the Investigator's first knowledge of the event. (If faxed within 1 calendar day of the Investigator's first knowledge, this form may serve as the initial notification.)

- Follow-up information, which may include copies of relevant subject records and other documents not available at the time the initial SAE Report Form was completed, must be sent to the Sponsor or Sponsor Designee as soon as available. Follow-up SAE reports may describe the evolution of the reported events and any new assessment of their outcome and/or relationship to treatment. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant subject/hospital records and pathology or autopsy reports.
- Investigators will receive copies of expedited safety reports that the Sponsor sends to regulatory agencies. The Investigator is responsible for fulfilling local reporting requirements to their IRB. Investigators will report events to their IRB in accordance with applicable standard operating procedures and/or local reporting requirements. Investigators must forward copies of the IRB notification to the Sponsor.

10.5.1 Follow Up of Adverse Events/Serious Adverse Events

All AEs/SAEs documented at a previous contact that are designated as not recovered/not resolved or recovering/resolving will be reviewed by the Investigator at subsequent contacts.

The Investigator will provide follow-up information for any SAE to the Sponsor or Sponsor designee as soon as it is available. The Sponsor or regulatory authorities may request additional information regarding an SAE.

All AEs will be followed until the resolution of AE, completion of the subject's participation, or study termination, whichever occurs first. Serious AEs will be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is no longer necessary.

Rules for AE/SAE follow-up apply to all subjects, including those withdrawn prematurely to the extent allowed by the subject's consent. The Investigator will ensure that follow-up includes further investigations consistent with appropriate medical management and subject consent to elucidate the nature and/or causality of the AE/SAE.

10.6 Pregnancy Reporting

If a female subject becomes pregnant at any time after the first dose of study treatment, she must be discontinued from study treatment immediately and followed by the Investigator at least until the outcome of the pregnancy is known (i.e., delivery, elective termination, spontaneous abortion, etc.). During the follow-up period, the Investigator must report on any subsequent treatments and the outcome of the pregnancy to the Sponsor. If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The Investigator must notify the Sponsor (via fax) within 24 hours of first learning of the occurrence of a pregnancy in a female patient or the sexual partner of a male patient, and provide the date of the last menstrual cycle. When the Investigator becomes aware of the pregnancy outcome, this information must also be reported to the Sponsor within 24 hours.

10.7 Additional Study-Specific Safety Reporting Requirements

In addition to the reporting requirements specified above, all unanticipated problems involving risk to subjects or others, SAEs, and all subject deaths associated with the study must be promptly reported to the US Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO) by phone ([301] 619-2165), e-mail (hsrrb@amedd.army.mil), or facsimile ([301] 619-7803).

In addition, the study's Independent Medical Monitor must review all unanticipated problems involving risk to subjects or others, SAEs, and all subject deaths associated with the study and provide an unbiased written report of the event to the USAMRMC ORP HRPO within 10 calendar days. At a minimum, the Medical Monitor should comment on the outcomes of the event or problem and, in the case of an SAE or a death, on the relationship to participation in the study. The Medical Monitor should also indicate whether he/she concurs with the details of the report provided by the Investigator. Reports for events determined by either the Investigator or the Medical Monitor to be possibly, probably, or definitely related to participation and reports of events resulting in death should be promptly forwarded to the HRPO. The Medical Monitor may not necessarily be on site during all study procedures but will remain in close contact with the Investigator during the conduct of the study and will be available by cell phone around the clock.

Complete reports may be emailed or faxed (e-mail: hsrrb@amedd.army.mil; facsimile: [301] 619-7803) or sent to the following address:

US Army Medical Research and Materiel Command
ATTN: MCMR-RPH
504 Scott Street
Fort Detrick, MD 21702-5012

11 DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

11.1 Recording of Data

The Investigator or personnel designated by the Investigator will perform primary data collection based on source-document or clinic records or other source documentation. All required study information must be recorded on the appropriate eCRF screens/forms. The eCRFs are considered complete when all data fields are completed. The Study Monitor will conduct 100% source data verification to ensure maximum data integrity before review and approval of each subject's eCRF. In addition, as the person ultimately responsible for the accuracy of all eCRF data, the Investigator will provide electronic endorsement that the data on the eCRFs are accurate and complete.

11.2 Data Quality Assurance

The eCRFs will be reviewed by a clinical monitor from the Sponsor or a representative of the Sponsor against the source notes for identification and clarification of any discrepancies. Automated quality assurance programs will be in place to identify discrepancies, such as missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be documented on electronic data clarification requests (eDCRs) and forwarded to the Investigator or study coordinator for resolution. All changes to the eCRFs will be tracked to provide an audit trail.

The Investigator must make study data accessible to the Study Monitor, to other authorized representatives of the Sponsor, and to the appropriate regulatory authority inspectors.

11.3 Data Management

The Sponsor in close collaboration with any designee will be responsible for:

- database creation and validation
- eCRF review and data validation
- query resolution
- data analysis and reporting

11.4 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB and agreed to by the Investigator. Deviations can have an impact on individual subjects or a small group of subjects and can involve

inclusion/exclusion or primary endpoint criteria. Deviations also occur when there is non-adherence to the protocol that results in a significant, additional risk to the subject, when the subject or Investigator has failed to adhere to significant protocol requirements and the subject was enrolled without prior sponsor notification and IRB approval, or when there is non-adherence to FDA regulations and/or ICH E6. Deviations from the protocol will be documented and reported to the IRB as required.

12 STATISTICAL METHODS AND PLANNED ANALYSES

12.1 General Considerations

This section describes the plan for the rules and conventions to be used in the analysis and presentation of data for study protocol 7288-us-101.

This plan may be revised during the study to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution that could affect planned analyses. These revisions will be based on blinded review of the data, and a final plan will be issued prior to database lock.

All available data will be included in data listings and tabulations. No imputation of values for missing data will be performed.

Percentages of subjects with AE or laboratory toxicities will be based on non-missing values.

A formal statistical analysis plan for the analysis and presentation of data from this study will be prepared before database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

Placebo-treated subjects will be pooled across all dose groups.

Statistical analysis will be performed by or under supervision of the Sponsor.

12.2 Determination of Sample Size

Sample size for this study was based upon qualitative considerations. No formal sample size calculations were performed.

The following table provides probabilities for observing at least one AE within any particular dose cohort, for various incidence rates and sample sizes.

Table 12-1: Probabilities for Observing Adverse Events

	Incidence Rate		
Sample Size	**0.02**	**0.10**	**0.30**
6	0.11	0.47	0.88
8	0.15	0.57	0.94
10	0.18	0.65	0.97

For example, if a rare event occurs 2% of the time, the probability that at least 1 subject complains of this event is 11% in any cohort with 6 subjects receiving AVI-7288.

Furthermore, the results from study 6003-us-101 showed low inter-subject variability for C_{max} (coefficient of variation [CV] range of 1.5 to 35.7%) and AUC_{0-24} (CV range of 5.1 to 32.7%) with 4 subjects per cohort suggesting the proposed sample size of 6 subjects per cohort receiving AVI-7288 is reasonable for this type of study.

12.3 Analysis Sets

All analyses except PK analyses will be performed using the Safety Set. If incorrect treatment is assigned, subjects will be analyzed according to the treatment they actually received for both analysis data sets.

12.3.1 Safety Set

The Safety Set will include all randomized subjects who receive any amount of study drug.

12.3.2 Pharmacokinetic Set

The Pharmacokinetic Set will include all randomized subjects who receive the full dose of study drug and for whom there are adequate PK samples from which to estimate PK parameters.

12.4 Demographics and Baseline Characteristics

Subject demographic data (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, BMI) will be listed for all subjects and summarized by dose group and for all subjects.

12.5 Subject Accountability

The number and percentage of subjects completing or prematurely discontinuing the study will be summarized by dose group. Reasons for premature discontinuation will be summarized.

12.6 Study Treatment Usage and Compliance

The total number of infusions administered as well as the cumulative exposure to study drug will be summarized by dose group.

12.7 Efficacy Analyses

Not applicable.

12.8 Safety Analyses

All subjects who are randomly assigned to a treatment group within each dose cohort and receive at least 1 dose of the study drug will be included in the safety and tolerability analyses. Unless otherwise noted, baseline for all quantitative safety measures (laboratory parameters, vital signs,

and 12-lead ECG measurements) will be defined as the last valid evaluation done before the study drug administration on Day 1.

Safety evaluations will be based on the incidence, intensity, and type of AE and clinically significant changes in the subject's physical examination findings, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented for all subjects who receive study drug, i.e., the safety set.

Abnormalities in clinical laboratory, vital signs, and ECG will be based on pre-defined normal ranges and will be tabulated by dose group showing subject counts and percentages.

12.8.1 Physical Examination and Vital Signs

Descriptive statistics will be provided to evaluate raw data and change from baseline at each scheduled time point. Normal reference ranges and pre-defined change abnormal results will be used in the summary of vital signs data. Results of physical examinations will be listed.

12.8.2 Clinical Laboratory Tests

Laboratory data will be summarized by the type of laboratory test. Normal reference ranges and pre-defined change abnormal results will be used in the summary of laboratory data. Raw data and change from baseline in clinical laboratory parameters will be summarized using descriptive statistics. Shift tables will be produced for selected laboratory parameters. A listing of subjects with any laboratory results outside the reference ranges will be provided.

Changes in renal function tests will be specifically analyzed to identify trends that may not be readily detectable in an analysis of group mean values over time. Specifically, at each time point, the number and percentage of subjects in each cohort with Grade 1, Grade 2, Grade 3 or Grade 4 toxicity serum creatinine levels will be presented. The number and percentage of subjects who have a >3-fold increase in UACR from predose on Day 1 to an absolute value of >30 mg/g will also be presented.

12.8.3 Adverse Events

The original terms used in the eCRF by Investigators to identify AEs will be coded using the current version of the Medical Dictionary of Regulatory Activities (MedDRA). The percentage of subjects with specific treatment-emergent AEs will be summarized for each treatment.

Special attention will be given to those subjects who have discontinued treatment due to an AE or who experienced a severe or a serious AE.

All AEs will be presented in a subject data listing.

12.8.4 Concomitant Medications

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. These data will be presented in a subject data listing.

12.8.5 Twelve-Lead Electrocardiograms

12-lead ECG variables will be evaluated by means of descriptive statistics for raw and change from baseline data, as well as by frequency tabulations. Normal reference ranges and pre-defined change abnormal results will be used in the summary of all ECG data. All important abnormalities from the ECG readings, including changes in T-wave morphology and/or the occurrence of U-waves versus baseline recordings, will be reported.

12.9 Pharmacokinetic Analysis

The PK analysis at the specified dose levels will be based on blood and urine samples for the AVI-7288-treated subjects.

Data will be listed for all subjects with available plasma concentrations per dose group and treatment. All concentrations below the quantification limit (BQL) or missing data will be labeled as such in the concentration data listings. BQL concentrations will be treated as 0 in the summary statistics and for the calculation of PK parameters.

Pharmacokinetic parameters for AVI-7288 will be calculated using non-compartmental analysis. Actual sampling times will be used in all final PK parameter estimations. Per-protocol times will be used to calculate mean plasma concentrations for graphical displays and summary tables.

C_{max} and T_{max} will be taken directly from the data. The elimination rate constant, λ_z, will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The range of data to be used for each subject and dose will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time. Other PK parameters will be calculated as described in Section 6.1.3. All PK calculations and figures will use validated software.

Listings of individual subject plasma concentrations, actual blood sampling times, and PK parameters and graphs of concentration vs. time will be prepared by dosing cohort. Plasma

concentrations and PK parameters will be summarized by and compared among dosing cohorts using descriptive statistics.

Dose proportionality for C_{max} and AUC(s) will be assessed visually by plotting these parameters (original and dose-normalized) against dose. Further statistical analyses may be performed to assess dose proportionality. Accumulation ratios for C_{max} and AUC(s) and time to steady state will also be assessed.

The terminal phase following 14 days of consecutive dosing (Day 14 profile) will be compared versus that following single dose (Day 1 profile) to assess the within-subject impact of multiple dosing on the elimination of AVI-7288.

In addition, the following PK parameters will be calculated from the urine levels of AVI-7288:

- Amount excreted for each defined urine collection time point
- Cumulative amount excreted over time (up to 1 day after last administration)
- Cumulative percentage of injected AVI-7288 excreted in the urine
- Calculated Cl_r (i.e., urinary clearance).

For each subject, renal clearance will be estimated as total amount of AVI-7288 that is excreted during a 24-hour sample collection period divided by AUC_{0-24}.

12.10 Interim Analyses

Interim analyses of safety will be performed on a per-cohort basis by the DSMB. The content of these analyses will be specified in the DSMB charter, which will be ratified by the independent members of the DSMB.

12.11 Other Statistical Issues

Additional analyses may be conducted. Any such analyses will be detailed in the SAP.

13 SPECIAL REQUIREMENTS AND PROCEDURES

13.1 Compliance with Ethical and Regulatory Guidelines

This study was designed and will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in conformance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) E6 guidance documents. The study will comply with the requirements that are enunciated in the US Code of Federal Regulations (CFR) related to the protection of human subjects (21 CFR Part 50), IRBs (21 CFR Part 56), INDs (21 CFR Part 312), electronic records and electronic signatures (21 CFR Part 11), and financial disclosure (21 CFR Part 54).

13.2 Institutional and Ethics Review

This study will be conducted in full compliance with the IRB regulations in 21 CFR 56. Before enrollment of subjects into the study, the protocol and informed consent documents will be reviewed and approved by an IRB that is in compliance with 21 CFR 56. Amendments to the protocol will be subjected to the same IRB review requirements as the original protocol. The Investigator will promptly notify the IRB and Sponsor of any serious or unexpected AEs or of any other information that might affect the safe use of the study drug during the study. A letter documenting the IRB approvals must be sent to the Sponsor before initiation of the study or before an amendment is instituted. All correspondence with the IRB should be retained in the study files.

13.3 Data Safety Monitoring Board

An independent DSMB will be assembled by the Sponsor and will consist of up to 4 physicians with relevant experience and expertise (including at least 1 with expertise in nephrology). The Sponsor will facilitate drafting and ratification of a DSMB charter; however, the content of the charter, including the specific safety monitoring that falls within the purview of the DSMB and the DSMB structure, frequency of meetings, remittance, procedures, and administrative support, must be approved by the members of the DSMB. The DSMB will evaluate the study experience and outcome of all treated subjects in an ongoing fashion, focusing on subject safety, and will convene at least once after each cohort, prior to escalation to the next dose level. The DSMB may convene more frequently if required based upon the safety experience of individual subjects.

Blinded study data will be provided to the DSMB but, if necessary, in light of an AE or pattern of AEs, the DSMB may ask for the blind to be broken to allow the members to ascertain whether continuation of the trial is acceptable and warranted. The DSMB will be responsible for

providing recommendations to the Sponsor concerning the advisability of dose escalation and continuation of the trial in the setting of a possible safety signal.

13.4 Informed Consent and Authorization for Use and Disclosure of Protected Health Information

Written informed consent and written authorization of use and disclosure of protected health information (PHI) from each subject must be obtained before any study-specific screening or baseline period evaluations are performed. One copy of the signed informed consent document and the signed authorization for use and disclosure of PHI will be given to the subject; the Investigator will retain the original copies of these documents.

The informed consent document and authorization for use and disclosure of PHI, which are prepared by the Investigator or the site, must be reviewed and approved by the Sponsor, and the IRB before initiation of the study. The informed consent document must contain the basic required elements of consent and additional elements, as applicable, as specified in 21 CFR 50.25. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508(b) in the US for valid authorizations.

13.5 Confidentiality

13.5.1 Data

All information regarding the nature of the proposed investigation that is provided to the Investigator by the Sponsor, the Sponsor's designee, or the Study Monitor, with the exception of information that is required by law or regulations to be disclosed to the IRB or the appropriate regulatory authority, must be kept in confidence by the Investigator in accordance with current Health Insurance Portability and Accountability Act (HIPAA) standards.

13.5.2 Subject Anonymity

The anonymity of participating subjects will be maintained to the extent required by applicable laws and in accordance with current HIPAA standards. Subjects will be identified by their initials and an assigned subject identification number on the eCRFs and other documents that are reviewed by the Study Monitor. The Investigator must maintain all documents related to the study that identify the subject (e.g., the signed informed consent document) in strict confidence, except to the extent necessary to allow auditing by the appropriate regulatory authorities, the IRB, the Study Monitor, or the Sponsor or its representatives.

13.6 Changes to the Conduct of the Study or Protocol

Changes to the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, doses, assessment variables, the number of subjects to be treated, or the subject selection criteria. Such changes must be documented as a protocol amendment by the Sponsor and must only be implemented upon joint approval of the Sponsor, Investigator, and IRB.

A protocol amendment must receive IRB approval before implementation. In parallel with the IRB-approval process, the protocol amendment will be submitted to the FDA as an amendment to the IND application. If a protocol amendment requires changes in the informed consent document, the revised document must be reviewed and approved by the Sponsor before review and approval by the IRB.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed by the Investigator as crucial for the safety and well-being of that subject may be instituted for that subject only. The Investigator will contact the Sponsor Medical Monitor as soon as possible regarding such a departure. These departures do not require preapproval by the IRB; however, the IRB and Sponsor Medical Monitor must be notified in writing as soon as possible in accordance with the IRB policies after the departure has been made; the HRPO must also be notified of any deviation to the protocol that may have an effect on the safety or rights of the volunteer or the integrity of the study. In addition, the Investigator will document the reasons for the protocol deviation and the ensuing events in the subject's eCRF. Documentation of IRB approval of any amendments must be returned to the Sponsor or designee.

13.7 Additional Study-Specific Requirements

Additional study requirements as specified in the "Guidelines for Investigators: Requirements for U.S. Army Medical Research and Materiel Command (USAMRMC) Headquarters Level Administrative Review and Approval of Research Involving Human Volunteers, Human Anatomical Substances, and/or Human Data" guidance document (dated 30 August 2010) not already addressed in the body of this protocol are included in Appendix V: Additional Study Information.

14 STUDY DOCUMENTATION AND ADMINISTRATIVE DATA

14.1 Case Report Forms

An eCRF is required and must be completed for each subject, with all required study data accurately recorded such that the information matches the data contained in medical records (e.g., physician's notes, clinic charts, and other study-specific source documents). The Investigator or designee (e.g., study coordinator) will be trained in the use of the study-specific eCRFs and will enter the data for each subject directly into the eCRFs.

Source documents will be filled out legibly and completely in ink. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the source documents will be crossed out with a single line, initialed and dated, and the correct entry, if appropriate, will be recorded. The original source documents will be provided to the Sponsor or designee. These source documents will be maintained in the Investigator's site file. Illegible or incomplete entries or entries needing additional explanation will be queried to the Investigator for clarification.

Data will be entered by the site onto the eCRFs. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the eCRFs should be corrected. Changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail, and should include the reason for change. Incomplete entries or entries needing additional explanation will be highlighted or queried to the Investigator for clarification.

The eCRFs will be reviewed and source verified by the Study Monitor (e.g., clinical research associate) during periodic site visits. During the data collection process, automated quality assurance programs will be in place to identify discrepancies, such as missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be documented on eDCRs and forwarded to the Investigator or study coordinator for resolution. The Investigator or study coordinator will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate. All changes to the eCRFs will be tracked to provide an audit trail. The Investigator has the final responsibility for the accuracy of all clinical data that are entered on the eCRFs and will be required to provide written endorsement that the data are accurate and complete via electronic signature.

14.2 Study Files

Documentation concerning Investigator data (e.g., a signed Form FDA 1572, curriculum vitae, and completed and signed Financial Disclosure Form), IRB data (including documentation of IRB approval and compliance), and clinical laboratory information, as well as the signed protocol page and a blank copy of the IRB-approved informed consent document and authorization, are among the critical documents required before study site initiation visit is to occur (see Appendix II: Requisite Documents for Approval of Study Site). Copies of these documents, as well as supplemental information, such as the Investigator's Brochure, responsibilities and obligations of Investigators and Sponsor, final protocol, and a detailed description of the Sponsor and Investigator responsibilities (see Appendix III: Responsibilities of Sponsors and Investigators) must be kept onsite in a special study file. This file also will contain a copy of the blank eCRFs (i.e., copies of blank data entry screens), subject accountability records, drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB correspondence, amendments to the protocol, information on monitoring activities, biological sample records, and SAE and safety reports.

14.3 Study Monitoring and Data Quality Control and Quality Assurance

Study monitors who have been selected and prequalified by the Sponsor for their experience, education and training, in accordance with the Sponsor's requirements and after having documentation of training in the applicable FDA regulations, ICH guidelines and GCP, and study-specific procedures and protocol, will ensure that the study is conducted and documented properly by carrying out the relevant activities, as outlined in GCPs (ICH E6, Section 5.18.4). The progress of the study will be monitored through:

- Periodic on-site visits
- Frequent telephone communications between the site (Investigator and study coordinator) and the Study Monitor(s), Sponsor Medical Monitor and AVI BioPharma
- Review of eCRFs, source documentation, and clinical records
- Following the approved monitoring plan

Sponsor representatives may accompany the Study Monitor to the site during scheduled visits.

Audits may be carried out by the Sponsor's representatives, and inspections may be performed by regulatory authorities or IRBs before, during, or after the study. The Investigator will allow and assist the Sponsor's representatives and any regulatory agency to have direct access to all

study records, eCRFs, subject medical records, and other source documentation, investigational product dispensing records and investigational product storage area, study facilities, and any other documents considered source documentation. Audit certificate(s) will be provided.

Representatives of the USAMRMC are also eligible to review research records.

14.4 Retention of Study Documents

The supporting documentation and administrative records all must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. Furthermore, in compliance with ICH E6, essential documents should be retained until 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 investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No study documents will be destroyed or moved to a new location without prior written notification to and approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records that are required to be maintained for the study should be transferred to an agreed-upon designee.

Subject records or other source data must be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If offsite archiving is used, all records should be retrieved and made available for review at the time of an audit or regulatory authority inspection.

14.5 Termination of Study or Study Site

If the Sponsor, the Investigator, the Sponsor Medical Monitor, the Study Monitor, IRB, or appropriate regulatory officials discover conditions arising during the study that indicate the study should be halted or that the study center should be terminated, appropriate action may be taken after consultation among the Sponsor, the Investigator, IRB and the Sponsor Medical Monitor.

Conditions that may warrant termination of the study or an individual site include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of the IRB or appropriate regulatory authorities such as the statement of the Investigator (Form FDA 1572), or 21 CFR Part 11, 50, 54, or 312
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, IRB, or regulatory authority
- Insufficient adherence to protocol requirements consistent with 21 CFR 312.60, or insufficient compliance with the signed agreement (Form FDA 1572), the general investigational plan (protocol), or the requirements of 21 CFR 312

Study termination and follow-up will be performed in compliance with the conditions set forth in the ICH E6 guideline on GCP (Sections 4.12, 4.13, 5.20, and 5.21) as well as 21 CFR 312.56(b), which requires a Sponsor to ensure an Investigator's compliance with the signed agreement (Form FDA 1572), the general investigational plan (protocol), or the requirements of 21 CFR 312 or other applicable parts and to promptly either secure compliance or discontinue shipments of the investigational new drug to the Investigator and end the Investigator's participation in the investigation.

14.6 General Information

The Investigator should refer to the associated most current and up-to-date Investigator's Brochure, the information that is provided during the study initiation visit, the information that is provided by the Study Monitor during routine monitoring visits, and the appendices of this protocol for further information on this investigational new product or details of the procedures that are to be followed during this study.

14.7 Dissemination of Study Results

The information that is developed during the conduct of this clinical study is considered to be strictly confidential. This information may be disclosed only as deemed necessary by AVI BioPharma. However, at the conclusion of this clinical study, a clinical study report will be prepared. In addition a manuscript will be prepared for publication in a reputable scientific journal under the direction of the Investigator and AVI BioPharma. AVI BioPharma and the

Investigator intend to publish and communicate the clinical study results, irrespective of positive or negative findings. Data generated for this study will be exclusively owned by AVI BioPharma, as detailed in the Clinical Trial Agreement. The study will be registered on ClinicalTrials.gov once appropriate approval has been received and before the first subject is enrolled.

14.8 Investigational Product Control

An accurate record of the use of the investigational product vials for each subject and each dose must be kept. The drug receipt records at the investigational site and documentation of administration of the investigational product doses will be used together to provide drug accountability.

At the conclusion of the study, information describing the study drug supplies (e.g., lot number) and their disposition must be provided for each subject. The product accountability records must be signed by the Investigator and a copy will be collected by the Study Monitor. At the conclusion of the study, all unused investigational product vials must be returned to AVI BioPharma or destroyed at the site according to the site's standard operating procedure(s).

14.8.1 Receipt of Investigational Product

An accurate record of the use of the investigational product vials for each subject and each dose must be kept. A proof of receipt, which details the quantity and description of the investigational product, will accompany the shipment from the Sponsor to the Investigator. This receipt must be signed, dated, and sent to the Sponsor or Sponsor designee within 24 hours after receipt, while retaining the original within the site pharmacy files. The Investigator must ensure that the investigational product is maintained in a controlled location, with limited access, and under appropriate storage conditions.

14.8.2 Disposition of Unused Investigational Product

All unused investigational products must be maintained under adequate storage conditions in a limited-access area. If any unused material is remaining upon completion of the study, the material will be returned to the Sponsor or destroyed only after the following has been completed:

- Accountability has been performed by a representative of the Sponsor.
- An Investigational Product Returns and Destruction Form has been completed by the pharmacist or designee and a copy provided to the Sponsor

14.8.3 Product Handling and Complaints Reporting

If there are any issues during the course of the study related to the quality of the investigational product, the Investigator, clinical site pharmacist or pharmacy designee should contact the Sponsor.

15 REFERENCES

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16 APPENDICES

16.1 Appendix I: Schedule of Study Events

Activity	Screening (up to D -21)	Confinement Period																	Outpatient Follow up	
		Check in D -1	First Dose D 1	D 2	D 3	D 4	D 5	D 6	D7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	Dis-charge D 16	D 21	D 42
Informed consent	X																			
Demographics	X																			
Height, Weight and BMI [a]	X	X																		
Review Inclusion/Exclusion Criteria	X	X	X																	
Medical history [b]	X	X	X																	
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment [c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[d]	X	X																		X
Urinalysis/Urinary parameters [e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Urinary biomarkers [e,g]		X	X		X				X			X				X				
12-lead ECG [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Vital signs [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [j]	X	X																X		
Serum pregnancy test [k]	X	X																		
Drug Screen[l]	X	X																		
FSH test [m]	X																			
HIV, HBV and HCV serology	X																			
Chemistry panel (Full = F, Limited = L) [n]	F	F	F	F	F	L	L	L	F	L	L	X	L	L	L	F			F	
Hematology	X	X	X	X	X				X			X				X			X	
Coagulation (PT/aPTT)	X	X														X				
Plasma pharmacokinetic sampling (Full = F, Trough = T) [o]			F	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F		
Urine pharmacokinetic sampling [p]			X													X	X			
Dose subject [q]			X	X	X	X	X	X	X	X	X	X	X	X	X	X				

[a] Height at Screening only; height and weight should be measured with shoes off, height should be recorded in cm, weight in kg.

[b] Complete medical history at screening including past blood donation history, tobacco use, and history of previous investigational drug/device study participation. Interim medical history at Check-in and immediately prior to dosing on Day 1 to capture safety findings that occur prior to subject dosing.

[c] Treatment-emergent AEs will be collected on an ongoing basis from initiation of dosing on Day 1 through completion of Day 42 (or time of early withdrawal as applicable). In addition, on dosing days (Days 1 through 14) the subject should be assessed for AEs immediately prior to and approximately 1 hour after dosing.

[d] Urine pregnancy testing is for women of childbearing potential only.

[e] When subject is confined to the unit on Days 1 through 16, urine should be obtained from first morning void.

[f] Urinalysis/urinary parameters including bilirubin, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, microscopy, urine microscopy including red blood cells, white blood cells, bacteria, yeast, epithelial cells and other abnormalities such as casts, crystals and renal tubular epithelial cells; Standard urinary parameters including quantitative albumin, total protein, creatinine.

[g] Urinary biomarkers including Kidney Injury Molecule-1 (KIM-1), cystatin C, and β2-microglobulin, each normalized to urine creatinine.

[h] 12-lead electrocardiogram (ECG) will be performed after the subject has been in the supine position for a minimum of 15 minutes. ECGs will be performed in triplicate (with at least 1 minute between each ECG) during Screening, on Day -1, and on Day 1 prior to dosing. On Dosing Days 1 through 14, ECGs will be performed a single time, approximately 1 hour after dosing.

[i] Vital signs (temperature, respiratory rate, pulse and blood pressure) should be measured after a minimum of approximately 5 minutes of rest at all times. On Days 1 through 14 vital signs should be measured pre-dose and then approximately 1 hour post-dose. On Days 15 and 16, vital signs should be measured approximately 24 and 48 hours after the last dose of study drug on Day 14. Temperature should be collected orally and recorded in degrees Celsius (°C).

[j] Complete physical examinations include assessment of general appearance; skin; lymph nodes; head, eyes, ears, nose and throat (HEENT); chest/lungs; cardiovascular; abdomen; musculoskeletal; and neurological. Note that focused physical examinations may be performed throughout the study as needed (e.g., to obtain further information related to an AE).

[k] Serum pregnancy testing is for women of childbearing potential only.

[l] Includes screen for use of alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, nicotine and cotinine; urine and/or blood testing may be performed according to the means available to the Phase 1 unit; if urine is used samples will be obtained prior to ECG.

[m] Follicle Stimulating Hormone (FSH) test performed on female subjects only to confirm post-menopausal status, as applicable.

[n] Full chemistry panel includes sodium, potassium, chloride, blood urea nitrogen, creatinine, calcium, glucose, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, albumin, total protein, cholesterol, and uric acid. Limited chemistry panel includes blood urea nitrogen and creatinine.

[o] Full plasma PK sampling will be performed at the following time points on Day 1: immediately pre-dose, at approximately 10 and 30 minutes post-dose, and at approximately 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours post-dose (collection of plasma 24-hours post dose will also serve as the

trough sample for Day 2). Plasma PK sampling will also be performed at the following time points on Day 14: immediately pre-dose on Day 14, at approximately 10 and 30 minutes post-dose, and at approximately 1, 1.5, 2, 4, 6, 8 12, 16, 24, 28, 32, 36, and 48 hours post-dose (collection of plasma pre-dose on Day 14 will also serve as the trough sample for that day). Plasma sampling will also be performed immediately prior to dosing on Days 3 through 13 for determination of trough values.

[p] Urine for PK sampling will be collected at the following time intervals on Day 1 and Day 14: pre-dose until completion of infusion, 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours post-dose. Subject will void within 30 minutes before dosing to empty bladder pre-dose, and then 4, 8, 12 and 24 hours ± 15 minutes post-dose to complete the preceding urine collection interval.

[q] Blinded study drug (AVI-7288 or placebo) administered by IV infusion over 30 minutes, starting at approximately the same clock time of dosing on Day 1.

16.2 Appendix II: Requisite Documents for Approval of Study Site

Clinical study material will be provided to the Investigators after they have submitted the following documents to the Study Monitor:

- Signed protocol and amendment(s), if applicable
- Signed Statement of the Investigator (From FDA 1572)
- Document indicating IRB review and approval of the final protocol and the informed consent document (to include name, address, and chairperson of the IRB)
- IRB committee composition as evidenced by documentation presented by the IRB
- Blank (unsigned) copy of the IRB-approved informed consent document
- Signed Investigator's Agreement and Letter of Confidentiality
- Clinical laboratory certification and normal ranges for tests that are performed in the laboratory for study assessments
- Curricula vitae for the Investigator and Sub-Investigator(s)
- Financial disclosure information for the Investigator and Sub-Investigator(s)

16.3 Appendix III: Responsibilities of Sponsors and Investigators

Sponsor (AVI BioPharma):

AVI BioPharma or designee will conduct a pre-investigation Site Selection Visit and/or Study Initiation Visit to:

- Establish the acceptability of the facility and staff and record the visit in a written report (i.e., memorandum or form) before study initiation.
- Discuss with the Investigator the proposed clinical study and supply them with the Investigator's Brochure and the draft protocol for their review and approval.
- Discuss with the Investigator the regulatory requirements with respect to informed consent, IRB approval of the protocol, protocol amendments, and changes to the informed consent document.
- Discuss with the Investigator their obligation to supply the Study Monitor with all study-related source documents (including IRB approval, IRB charter or equivalent, IRB membership and qualifications, protocol amendments, informed consent document, and consent changes), and all pertinent correspondence to and from the IRB.

AVI BioPharma or designee will conduct periodic on-site visit(s) to:

- Assure adherence to the protocol and applicable regulatory requirements.
- Review eCRFs and source documentation (e.g., clinic records) for accuracy and completeness of information.
- Examine pharmacy records for documentation of quantity and date of receipt of investigational drug, dispensation, and accountability data for product administration to each subject, loss of materials, contamination, and unused supplies.
- Record and report (summarize) observations on the progress of the study and continued acceptability of the facilities and staff, and prepare an on-site visit report.
- Review Investigator files for required documents (e.g., protocols; protocol amendments; Investigator's Brochure; IRB approval of protocols, amendments, and informed consent document; IRB membership; and communications to and from the IRB and the Study Monitor).

Investigator

The Investigator must assure the Sponsor that the IRB:

- Has the authority delegated by the parent institution and found in the IRB by-laws, operation guidelines, or charter to approve or disapprove clinical studies and protocols, including informed consent and other documents (e.g., protocol amendments and information to be supplied to subjects concerning informed consent).

- Complies with proper personnel make-up of the IRB as specified in 21 CFR 56.107.
- Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them.
- Maintains files that contain (a) documentation of its decisions, such as are found in IRB minutes and correspondence, (b) written guidelines or by-laws governing IRB functions, (c) protocol, (d) protocol amendments, (e) approved informed consent document and other information to be supplied to the subject, and (f) correspondence between the IRB and Investigator (e.g., consent changes, protocol amendments).

The Investigator must assure the Sponsor that the informed consent document for a subject:

- Includes the basic elements and any additional elements of informed consent that are appropriate in accordance with 21 CFR 50.25.
- Meets ICH guidelines as defined in ICH E6 Section 4.8: Informed Consent of Study Subjects.
- Has been approved by the IRB, including (when required) information to be given to the subject regarding the study in which he is enrolled.
- Has been signed and dated by the subject, a trained staff member who obtains consent, and the Investigator, and that a copy has been given to the subject.

The Investigator (or designated pharmacist) must assure the Sponsor that:

- Adequate and accurate written records show receipt, dispensation, and disposition of all product supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each subject.
- Purpose and reasons are given in written records for product disposal (e.g., the amount contaminated, broken, or lost) and the quantity that was returned to the Sponsor.

The Investigator must assure the Sponsor that:

- The completed eCRF accurately reflects the clinical records and original source documents for each subject.
- The eCRFs, source documentation, and clinical records will be accessible to the Study Monitor at all times.

The Investigator must assure the quality, integrity, and content of his or her files, which will be subject to review by the Study Monitor and the appropriate regulatory authority inspectors. The files must contain, at a minimum the following:

- Investigator's Brochure
- Investigator's Obligations in the US, including the following:
  - 21 CFR Part 312.60-62, 64, 66, and 68 (Responsibilities of Investigator).
  - 21 CFR Part 50 (Protection of Human Subjects)

- International Conference on Harmonisation, GCP, Consolidated Guidelines (E6)

- IRB-approved protocol and protocol amendments
- Blank eCRFs (screen shots and amendments to eCRF)
- Statement of Investigator Forms (copy of signed Form FDA 1572, and a copy of each revised form if required by the regulatory agency) and current curricula vitae and financial disclosure information for each Investigator and Sub-Investigator
- IRB documents including the following:
  - IRB membership, and qualifications of each member
  - IRB letter of approval of protocol and informed consent form and letters of approval of protocol and informed consent form amendments
  - Investigator's continuing review (at a minimum annual report) to the IRB
  - IRB continuing review and approval of protocol
  - Reports to IRB of deaths and SAEs
  - Notification to IRB of study completion and Investigator's final report
  - IRB approval of advertisements for subject recruitment (if applicable)
  - All additional correspondence with the IRB
- IRB-approved informed consent document (all versions) and information to be supplied to the subject
- Study Staff Delegation of Authority Log
- Subject accountability records including the following:
  - Subject screening log
  - Subject identification code list (screening and randomization number as applicable)
  - Original signed informed consent documents
  - A note stating the location of the physical storage media (CD-ROM, USB flash drive, etc.) containing the eCRFs and electronic Data Clarification Requests (eDCRs)
- Clinical study material records including the following:
  - Receipt date, quantity, and batch or lot number
  - Disposition dates and quantity administered to each subject.
  - Inventory records (including temperature log if relevant to storage requirements)
  - All correspondence related to clinical study material
- Serious Adverse Events/Safety Reports
  - Copies of signed Serious Adverse Event Reporting Forms
  - All correspondence concerning SAEs, including the MedWatch Form FDA 3500A
- Biological sample inventory forms and correspondence with the analytical laboratory
- Monitoring activities
  - Monitoring Log (should include all visits [i.e., study site initiation, periodic, and

termination visits])
- Telephone contact reports
- Site initiation visit reports and general correspondence
- All correspondence between the Study Monitor, Sponsor, and the site
- All correspondence within the site concerning the protocol

- Documents and records must be retained by the Investigator:
  - At study completion all eCRF data will be copied onto a non-rewritable CD-ROM. This disc will be presented to the Investigator. The supporting documentation and administrative records all must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
  - In compliance with ICH E6, essential documents should be retained until 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 investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No study documents will be destroyed or moved to a new location without prior written notification of and approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records that are required to be maintained for the study should be transferred to an agreed-upon designee.
  - Audit trails for electronic documents must be retained for a period at least as long as that required for the subject electronic records to which they pertain. The Investigator must retain either the original or a certified copy of audit trails.

16.4 Appendix IV: Investigator Signature Page

I confirm that I have read and understand this protocol. I agree to conduct this clinical study according to the protocol, including any protocol amendments that have been mutually agreed to in writing and approved in advance by the Institutional Review Board. I also agree to conduct this study in compliance with the Principles of Good Clinical Practice as defined by federal, state, and local laws and regulations, as well as with the requirements of the appropriate Institutional Review Board, and the appropriate International Conference on Harmonization guidelines.
Investigator Signature Date
Investigator Name (please print or type)

16.5 Appendix V: Additional Study Information

Study Center

SNBL Clinical Pharmacology Center, Inc. (SNBL) is a Phase 1 facility located in Baltimore, Maryland. SNBL has a separate subject waiting room, 5 examination rooms and 2 PK laboratory rooms, each with a centrifuge, -20°C and -70°C freezers. SNBL has the capacity to hold 96 inpatient subjects in 2 confinement areas. The facility is equipped with (Phillips) blood pressure and 12-lead ECG machines, (Baxter 6201) IV pumps, a wireless telemetry machine that can monitor up to 16 subjects (in one of the confinement areas), a (Phillips) pulse oximetry machine/monitor, and a weight/height scale.

The site is also equipped with 2 crash carts, all shift RN's are both Basic Life Support Training (BCLS) and Advanced Cardiac Life Support training (ACLS) certified. In addition, SNBL hires RNs exclusively with critical care experience. If they use PRN or agency trained RNs these requirements still apply. SNBL non-clinical staff also are trained in BCLS. SNBL is able to maintain ICU conditions for a short period of time while calling 911 and awaiting transfer to the local hospital, which is only one block away. All equipment is inspected and calibrated regularly. All source documents, the regulatory binder and other study documents are kept inside a secured data records room.

All investigational products are stored under the appropriate environmental conditions in a secure location in the SNBL-CPC Pharmacy. All investigational products have a dedicated space in the pharmacy to avoid trial contamination and are stored in a locked cabinet or a locked refrigerator in the pharmacy. The environmental conditions of the pharmacy and the temperature of the refrigerator located in the pharmacy are monitored by the REES Scientific Monitoring System.

Access to the Pharmacy is restricted to the pharmacy staff **only** and access is controlled via proxy card through the REES Scientific Monitoring System.

Key Study Personnel

Key study personnel and their roles and responsibilities are listed below.

Personnel	Role	Responsibilities
Dan Rudin, M.D. SNBL Clinical Pharmacology Ctr. 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: drudin@snbl-cpc.com	Principal Investigator	Recruitment Informed consent Screening Medical history Physical examination Evaluation of adverse events Review of clinical laboratory results Review of entry criteria / Determination of eligibility Query resolution IRB correspondence CRF sign-off Administration of investigational product
Mohamed Al-Ibrahim, MB ChB, FACP SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: Mal-ibrahim@snbl-cpc.com	Sub-investigator	Recruitment Informed consent Screening Medical history Physical examination Evaluation of adverse events Review of clinical laboratory results Review of entry criteria Query resolution IRB correspondence Administration of investigational product
Masaru Kaneko, M.D., CPI SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: mkaneko@snbl-cpc.com	Sub-investigator	Recruitment Informed consent Screening Medical history Physical examination Evaluation of adverse events Review of clinical laboratory results Review of entry criteria Query resolution Administration of investigational product

Personnel	Role	Responsibilities
Patrick Wilcox SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: pwilcox@snbl-cpc.com	Project Manager (Primary Site Contact)	Obtain Consent Notify P.I. of abnormal lab results Specimen processing Shipment of samples Complete CRFs Dispense meals Update essential documents Administrative duties Recruiting/telephone screening Trainer Recruitment Informed consent Screening Conduct of study procedures (ECG, vital signs, phlebotomy) CRF completion Query resolution
Anastasia Dolgovskij, BS SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: adolgovskij@snbl-cpc.com	Study coordinator	Recruitment Informed consent Screening Conduct of study procedures (ECG, vital signs, phlebotomy) CRF completion Query resolution Update essential documents
Olajumoke Allison, Pharm D. SNBL Clinical Pharmacology Center 800 West Baltimore St. Baltimore, MD 21201 Tel: 800-690-9110 Fax: 410-706-8963 Email: oallison@snbl-cpc.com	Pharmacist	Study drug accountability Study drug preparation Verification of study drug Study drug dispensing

In the event that the key study personnel listed are unable to fulfill the roles and responsibilities listed above, a qualified alternate will be assigned. Other study responsibilities, such as study monitoring and data analysis, have been delegated to the Contract Research Organization by the Sponsor.

Study Recruitment

Prospective subjects will learn about the opportunity to participate in this trial primarily through their registration in the clinic database, but also through general information about early phase

studies on the clinic internet site, and advertising media in the community such as newspaper, radio, television, and billboards. The phone screen script that will be used to call prospective subjects from the clinic database will be preapproved by the IRB. Candidates who call the recruitment center will be asked a series of questions related to basic study inclusion/exclusion criteria. Subjects who meet basic study requirements discussed during the phone screening will then be offered a screening appointment at the clinic.

Before any screening procedures are performed at the clinic, candidates will be consented using the current IRB-approved informed consent form. Subjects will then be tested by investigator-delegated staff to determine if they meet the study inclusion/exclusion criteria outlined in the protocol. The Investigator or Sub-Investigator will review the screening results, and subjects who pass all screening criteria may then be invited to participate in the study.

Consent Process

The consent process will afford potential subjects complete privacy and adequate time for decision-making.

Subject Compensation

Subjects enrolled in this study will be compensated for study participation. The compensation plan will be reviewed by the IRB, who will ensure that the compensation plan is fair and does not provide undue inducement. The detailed, prorated compensation plan will be outlined in the IRB-approved informed consent.

Study Laboratories

The following laboratories will be performing the study evaluations. No samples will be kept for future use. The samples will be analyzed and disposed as per the individual laboratory policy and procedures.

Laboratory	Evaluations
SNBL Clinical Pharmacology Center, Inc. Clinical Laboratories 800 West Baltimore Street 5th and 6th Floor Baltimore, Maryland 21201	HBV, HCV and HIV serologies Core chemistry tests Core hematology tests Urinalysis Standard urinary parameters PT/aPTT Reticulocyte count Complement levels Serum pregnancy test
Quest Diagnostics Incorporated 1901 Sulphur Spring Road Baltimore, Maryland 21227	C3 and C4
Helix Diagnostics Inc. 505 South Rosa Road #30A Madison, WI 53719-1276	Plasma and urine AVI-7288 levels
Esoterix Clinical Trials Service 750 Walnut Avenue Cranford, New Jersey 07016	B2 Microglobulin
Esoterix Clinical Trials Services 5300 McConnell Ave. Los Angeles, CA 90066	Cystatin C KIM 1

All primary data, or copies thereof (e.g., laboratory records, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the study site archives and may be reviewed by the United States Army Medical Research and Material Command.

Continuing Review and Final Report

A copy of the approved continuing review report and the local IRB approval notification will be submitted to the Human Research Protection Office (HRPO) as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the HRPO as soon as these documents become available.

Sensitive Information

Disclosure of sensitive information about potential study participants including positive HIV, hepatitis, or tuberculosis test results, illegal residency, child or spousal abuse, or participation in other illegal activities will be handled in accordance with applicable State Law.

Protocol 7288-us-101

A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AVI-7288 in Healthy Adult Volunteers

Statistical Analysis Plan
FINAL
17 January 2014

Sarepta Therapeutics, Inc.
215 First Street, Suite 7
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SIGNATURE PAGE

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TABLE OF CONTENTS

1. INTRODUCTION

This analysis plan summarizes the planned analysis and presentation of the safety and tolerability data from the Sarepta, Inc. Protocol 7288-us-101: "A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics (PK) of AVI-7288 in Healthy Adult Volunteers".

The investigational product is AVI-7288 which will be diluted with 150 mL of normal saline into an intravenous (IV) bag to prepare a double-blind infusion. Study drug will be administered in 150 mL of normal saline as an IV infusion over 30 minutes. Study drug will be administered at approximately the same time each day for 14 days.

2. STUDY OBJECTIVES

The objectives of the study are:

- To evaluate the safety and tolerability of 14 once-daily IV infusions of ascending doses of AVI-7288 compared to placebo in healthy male and female subjects
- To evaluate the PK of 14 once-daily IV infusions of ascending doses of AVI-7288 in healthy male and female subjects

3. STUDY OVERVIEW

3.1. Study Design

This study is designed to evaluate the safety and tolerability of 14 once-daily IV infusions of ascending doses of AVI-7288 compared to placebo in healthy male and female subjects. The study is also designed to evaluate the PK of 14 once-daily IV infusions.

This is a Phase 1, randomized, double blind, placebo-controlled, multiple-dose, dose-escalation study to assess the safety, tolerability, and PK of AVI-7288 in healthy adult volunteers.

Up to 40 subjects will be randomized to 5 cohorts of 8 subjects each. Within each cohort, 6 subjects will receive AVI-7288 and 2 will receive placebo once daily for 14 days. Every effort will be made to include an equal number of male and female subjects in each cohort. The dose of AVI-7288 will be escalated in each sequential cohort as follows: 1 mg/kg, 4 mg/kg, 8 mg/kg, 12 mg/kg, and 16 mg/kg. Cumulative safety data through Day 21 for each cohort will be reviewed by an independent DSMB prior to dosing of the next dose cohort.

All subjects will be confined to the study center from 1 day prior to the first dose of blinded study drug (AVI-7288 or placebo) until 48 hours after the last dose, i.e., from Days -1 through 16. Subjects will return to the study center for safety evaluations 7 and 28 days post-last dose on Days 21 and 42, respectively.

3.1.1 Randomization and Blinding

All subjects, the Investigator, study staff, and Sponsor/Contract Research Organization Personnel will be blinded to whether the subject is receiving active study drug or placebo, except an unblinded statistician who will produce the actual randomization schedule and an unblinded site person(s) who is designated and authorized to dispense study drug according to the randomization code. A second individual who is authorized to verify the dose and assignment will also be unblinded to the subject's treatment assignment. Neither of these individuals will have interaction with the subjects, and both will be instructed not to divulge the randomization assignment to others under any circumstance, unless directed to do so by the Investigator in the interests of the subject's safety.

The prepared active and placebo infusions will be visually indistinguishable.

AVI-7288 for injection and matching placebo solution will be supplied blinded. Each unit of drug for infusion will contain either active or placebo ingredients according to the blinding or randomization code.

Subjects will be randomized sequentially in successive cohorts. Within each cohort, subjects will be randomized in a 3:1 ratio (3 active:1 placebo).

Randomization is based upon unstratified permuted block randomization with a block size of 4 or 8. The block size will be randomly selected by the unblinded statistician at the time the actual randomization schedule is produced. Prior to the time the study is

unblinded, the block size will only be known by the unblinded statistician who will produce the actual randomization schedule.

3.2. DSMB Safety Analyses

Interim safety analyses, blinded to the Sponsor, will be performed by an independent Data Safety Monitoring Board (DSMB) following a DSMB charter. The DSMB will review the clinical, laboratory, and AE data to evaluate the study safety of all treated subjects after each cohort.

Blinded study data will be provided to the DSMB; however, if adverse event(s) (AEs) or a pattern of AEs raise a safety concern, the DSMB may ask for the blind to be broken to allow the members to ascertain whether continuation of the trial is acceptable and warranted. In this case, an unblinded independent statistician otherwise unaffiliated with the study and its conduct will coordinate provision of the requested data to the DSMB. The DSMB will be responsible for providing recommendations to the Sponsor concerning the advisability of dose escalation and continuation of the trial in the setting of a possible safety signal.

3.3. Number of Study Sites

This is a single center study.

3.4. Overall Time and Events Schedule

The Schedule of Events is displayed in Table 1. Greater detail concerning the schedule of events can be found in the protocol.

Table 1: Schedule of Events

Activity	Screening (up to D -21)	Confinement Period																	Outpatient Follow up	
		Check-in (Day -1)	First Dose (Day 1)	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 16	D 21	D 42
Informed consent	X																			
Demographics	X																			
Height, Weight, and BMI [a]	X	X																		
Review Inclusion/Exclusion Criteria	X	X	X																	
Medical history [b]	X	X	X																	
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment [c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [d]	X	X																	X	X
Urinalysis/Urinary parameters [e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinary biomarkers [e,g]		X	X		X				X			X				X		X	X	X
12-Lead ECG [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Vital signs [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [j]	X	X																X		
Serum pregnancy test [k]	X	X																	X	X
Drug Screen [l]	X	X																		
FSH test [m]	X																			
HIV, HBV and HCV serology	X																			
Chemistry panel (Full = F, Limited = L) [n]	F	F	F	F	F	L	L	L	F	L	L	F	L	L	L	F	F	F	F	F
GFR, based on MDRD equation	X	X	X						X			X				X		X	X	X
Serum cystatin C	X	X	X						X			X				X		X	X	X
Hematology	X	X	X	X	X				X			X				X			X	X
Coagulation parameters (PT/aPTT)	X	X														X				
Plasma pharmacokinetic sampling [o]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine pharmacokinetic sampling [p]			X													X				
Dose subject [q]			X	X	X	X	X	X	X	X	X	X	X	X	X	X				

a. Height at Screening only; height and weight should be measured with shoes off, height should be recorded in cm, weight in kg.
b. Complete medical history at screening including past blood donation history, tobacco use, and history of previous investigational drug/device study participation. Brief medical history at check-in and immediately prior to dosing on Day 1 to capture safety findings that occur prior to subject dosing.
c. Treatment-emergent AEs will be collected on an ongoing basis from initiation of dosing on Day 1 through completion of Day 42 (or time of early withdrawal as applicable). In addition, on dosing days (Days 1 through 14) the subject should be assessed for AEs immediately prior to and approximately 1 hour after dosing.
d. Urine pregnancy testing is for women of childbearing potential only.
e. When subject is confined to the unit on Days 1 through 16, urine should be obtained from first morning void.
f. Urinalysis/urinary parameters including bilirubin, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, microscopy, urine microscopy (including RBC, WBC, bacteria, yeast, epithelial cells and other abnormalities such as casts, crystals and renal tubular epithelial cells), quantitative albumin, total protein, and creatinine.
g. Urinary biomarkers including KIM-1, cystatin C, and β2-microglobulin, each normalized to urine creatinine.
h. 12-lead ECG will be performed after the subject has been in the supine position for a minimum of 15 minutes. ECGs will be performed in triplicate (with at least 1 minute between each ECG) during Screening, on Day -1, and on Day 1 prior to dosing. On Dosing Days 1 through 14, ECGs will be performed a single time, approximately 1 hour after completion of dosing.
i. Vital signs (temperature, respiratory rate, pulse and blood pressure) should be measured after a minimum of approximately 5 minutes of rest at all times. On dosing days, all vital signs will be collected pre dose and approximately 1 hour after initiation of dosing In addition, on Dosing Days 1 and 2, blood pressure will be measured 10 and 30 minutes after initiation of dosing; continued measurement of blood pressure at 10 and 30 minutes after initiation of dosing after Day 2 is at the discretion of the Investigator. On Days 15 and 16, vital signs should be measured approximately 24 and 48 hours after the last dose of study drug on Day 14. Temperature should be collected orally and recorded in degrees Celsius (°C).
j. Complete physical examinations include assessment of general appearance; skin; lymph nodes; HEENT; chest/lungs; cardiovascular; abdomen; musculoskeletal; and neurological. Note that focused physical examinations may be performed throughout the study as needed (e.g., to obtain further information related to an AE).
k. Serum pregnancy testing is for women of childbearing potential only.
l. Includes screen for use of alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, nicotine and cotinine; urine and/or blood testing may be performed according to the means available to the Phase 1 unit; if urine is used samples will be obtained prior to ECG.
m. Follicle Stimulating Hormone (FSH) test performed on female subjects only to confirm post-menopausal status, as applicable.
n. Full chemistry panel includes sodium, potassium, chloride, BUN, creatinine, calcium, glucose, ALT, AST, GGT, alkaline phosphatase, lactate dehydrogenase, total bilirubin, amylase, albumin, total protein, cholesterol, and uric acid. Limited chemistry panel includes BUN and creatinine.
o. Full plasma PK sampling will be performed at the following time points on Day 1: immediately pre-dose, at approximately 10 and 30 minutes after completion of dosing, and at approximately 1, 1.5, 2, 4, 6, 8 12, 16, and 24 hours after completion of dosing (collection of plasma 24-hours post dose will also serve as the trough sample for dose 1). Plasma PK sampling will also be performed at the following time points on Day 14: immediately pre-dose, at approximately 10 and 30 minutes after completion of dosing, and at approximately 1, 1.5, 2, 4, 6, 8 12, 16, 24, 28, 32, 36, and 48 hours after completion of dosing. Plasma sampling will also be performed immediately prior to dosing on Days 3 through 13 for determination of trough values.
p. Urine for PK sampling will be collected during the following time intervals on Day 1 and Day 14: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after initiation of dosing. Subject will void within 30 minutes before dosing to empty bladder pre-dose, and then at 4, 8, 12 and 24 hours after initiation of dosing to complete the preceding urine collection interval.

q. Blinded study drug (AVI-7288 or placebo) administered by IV infusion over 30 minutes, starting at approximately the same clock time of dosing on Day 1.

3.5. Analysis Variables

Subject Disposition

- Subjects completing and/or subjects who were discontinued by cohort.
- Study drug exposure. This will be characterized by calculating, for each subject, the total amount of medication infused during the study and the time in days between the first dose and the last dose.
- Demographics and Baseline Characteristics
- Age, weight, height, body mass index (BMI), gender, ethnicity, and race.

For the purposes of the demographic summaries, weight will be the last available measurement taken before the first study drug administration.

BMI will be calculated as BMI = Weight (kg) / Height $(m)^2$. Any measurements in other units will be converted to kilograms and meters prior to the calculation. Weight (kg) = weight (lb)/2.2. Height (m) = height (inches)*0.0254.

All continuous baseline characteristics will be calculated from the last non-missing value prior to the first study drug administration.

- Medical history will be coded using MedDRA 14.0.

3.5.2 Prior and Concomitant Medication

A prior medication is any medication taken prior to the first study drug administration. A concomitant medication is any medication that is taken after the first study drug administration. Prior and concomitant medications will be coded using the March 2011 version of the World Health Organization classification for therapeutic class and drug name (WHO Drug Dictionary Enhanced).

3.5.3 Safety Variables

The safety and tolerability of AVI-7288 will be assessed through:

- A review and evaluation of the frequency and severity of AEs, serious adverse events (SAEs), and discontinuations due to AEs. Adverse events are coded using MedDRA (version 14.0) and are reported by primary System Organ Class (SOC) and Preferred Term Name (PT).

  AEs will be classified as treatment-emergent AE (TEAE) and non-emergent. TEAEs are those events that develop or worsen during the on-treatment period. Non-emergent events are those that develop during the pre-treatment period.

- Safety laboratory tests including hematology, coagulation, serum chemistry (including serum cystatin C), urinalysis, and urinary biomarkers (including urinary cystatin C, KIM-1, and β2-microglobulin each normalized to urine creatinine).
- Estimated GFR, based on the Modification of Diet in Renal Disease (MDRD) equation.

- Vital signs.
- Physical examination.
- 12-lead electrocardiograms (ECGs).

3.5.4 Pharmacokinetic Endpoints

Pharmacokinetic analysis will be the responsibility of the Sponsor.

Pharmacokinetic parameters to be estimated from plasma concentration-time data, using actual sampling times, include:

C_{max}	observed maximum plasma concentration (ng/mL)
T_{max}	time to reach the observed maximum plasma concentration (hr)
AUC_{τ}	area under the concentration-time curve calculated using the trapezoidal method over the dosing interval (24 hours) (ng*hr/mL)
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration C_{last} (ng*hr/mL)
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated according to the following equation: $AUC_{\infty} = AUC_{last}t + C_{last}/\lambda_z$ (ng*hr/mL) where C_{last} is the last measurable concentration and λ_Z is the apparent terminal phase elimination rate constant AUC will be reported if $t_{1/2,\lambda}$ is calculable and if C_{last}/λ_z represented 30% or less of the AUC value. AUC values where C_{last}/λ_z is less than 30% but equal to or greater than 20% of the AUC value will be flagged in the report.
MRT_{∞}	mean residence time, calculated as $AUMC_{\infty}/ AUC_{\infty}$
AUC_N	area under the concentration-time curve (AUC_{τ} or AUC_{∞}) normalized by the dose
$\%AUC_{\infty,ext}$	percentage of AUC_{∞} obtained by extrapolation, calculated by the following equation: $$\frac{AUC_{\infty} - AUC_{last}}{AUC_{\infty}} \times 100$$
$t_{1/2,\lambda}$	elimination half-life associated with the terminal slope (λ_Z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_Z$
λ_Z	first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve

$C_{max,ss}$	maximum plasma concentration during a dosing interval at steady state
C_{trough}	trough plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose
Swing (%)	$[(C_{max} - C_{min})/C_{min}]*100$
$C_{avg,ss}$	average plasma concentration at steady state, calculated as AUC_{τ}/τ
CL_{ss}	total clearance of drug at steady state
V_{ss}	apparent volume of distribution at steady state, calculated as $MRT_{\infty}*CL_{ss}$
Acc Ratio	accumulation for C_{max} and AUC estimated by dividing the PK parameter on Day 14 by the same parameter on Day 1

In addition, the following PK parameters will be calculated, whenever possible, for each subject based on the urine levels of AVI-7288 treated subjects:

- Amount excreted for each defined urine collection time point
- Cumulative amount excreted over time (up to 1 day after last administration)
- Cumulative percentage of injected AVI-7288 excreted in the urine
- Calculated Cl_R (i.e., urinary clearance)

Other PK parameters may be added as appropriate. PK calculations will be performed, if appropriate, using commercial software such as WinNonlin (Pharsight Corp., version 5.2 or higher). PK analysis will use actual times as recorded on the electronic case report form (eCRF).

4. STATISTICAL METHODS

4.6. Analysis Sets

4.6.1 Safety Set

The safety set will include all randomized subjects who receive any amount of study drug. Analyses performed on the safety set will be according to the dose actually received.

4.6.2 Pharmacokinetic Set

The Pharmacokinetic Set will include all randomized subjects who receive the full dose of study drug and for whom there are adequate PK samples from which to estimate PK parameters. Analyses performed on the PK set will be according to the dose actually received.

4.7. Handling of Missing Data

Imputation of missing data will not be performed unless otherwise specified. Descriptive statistics will be based upon reported data.

4.8. Conventions and Methods

This section details general conventions to be used for the statistical analyses. Departures from these general conventions will be specified in appropriate sections.

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, median, standard deviation (SD) or as appropriate the standard error of the mean (SE), minimum, and maximum values for continuous variables.
- All mean and median values will be formatted to a precision of 1 more decimal place than the measured value on the electronic case report form (eCRF). Standard deviation (SD) and SE values will be formatted to a precision of 2 more decimal places than the measured value on the eCRF. Minimum and maximum values will be presented with the same precision as the measured value on the eCRF. Percentages will be presented to a precision of 1 decimal place.
- The number and percentage of responses will be presented in the form XX (XX) where the percentage is in the parentheses. Unless otherwise specified, the denominator for percentages will be the number of subjects in a given dose group within the analysis population of interest.
- Baseline is defined as the last available value before dosing, or the mean of the Day -1 and Day 1 pre-dose values, as appropriate.
- Change from Baseline will be calculated for the confinement period and the outpatient follow-up period as follows:

  $$\textit{Change from Baseline} = \textit{Post-Baseline value} - \textit{Baseline value}$$

- Study Day will be defined as Event Date - First Dose Date + 1.

- Study day will appear in the data listings as appropriate.
- Events will be assigned to visit based upon the eCRF page the event was reported on.
- Date variables will be formatted as DDMMYYYY for presentation. In the case of missing day, month, and/or year information, "UN" will be presented. For example, a date with a missing month and day will be presented as UNUNYYYY.
- AEs with missing relationship or severity will be presented as "Severe" or "Related", respectively; however, missing values will be presented in the data listings as missing.
- For the purpose of calculating duration of an event with a missing day but known month and year, the first of the month will be used. For example 01MMYYYY will be used for UNMMYYYY.
- For the purpose of data listings and descriptive summaries, the placebo group will include all subjects who received placebo across all cohorts. The following labels will be used:
    - Placebo
    - 1 mg/kg
    - 4 mg/kg
    - 8 mg/kg
    - 12 mg/kg
    - 16 mg/kg
    - All AVI-7288 (select Summary tables)
    - All Subjects (select Summary tables)
- SAS® Version 9.2 or higher will be the statistical software package used for all data analysis.

4.9. Statistical Analyses

4.9.1 Protocol Deviations

A listing and summary of protocol deviations will be provided. The deviation listing will be based on the blinded review of the study data prior to locking the database and will include the nature of the deviation (e.g. inclusion/exclusion, prohibited therapies) and information on whether the Sponsor or Principal Investigator had permitted the deviation.

4.9.2 Subject Disposition

The number and percentage of subjects completing or prematurely discontinuing the study will be summarized by dose group. Reasons for premature discontinuation will also be summarized.

Subject accountability and subject eligibility (including inclusion/exclusion criteria) will be presented in data listings

4.9.3 Demographic and Baseline Characteristics

Demographic characteristics including age (years), race, ethnicity, gender, and Baseline characteristics including height (cm), weight (kg), and BMI (kg/m^2) will be summarized by dose group and overall. Demographic data and Baseline characteristics will be presented in the data listings.

4.9.4 Prior and Concomitant Medications

All Prior and Concomitant medications will be presented in a subject data listing.

4.9.5 Medical History

Medical history will be coded using MedDRA v14.0. Medical history data will be listed.

4.9.6 Dosing

The cumulative exposure to AVI-7288, total volume of drug administered (mL) and the total number of infusions received will be summarized by dose group. Dosing information will be provided in a listing.

4.9.7 Safety

Safety analyses will be descriptive in nature.

4.9.7.1. Adverse Events

Only TEAEs will be summarized. For all AE tables, the number and percent of subjects reporting AEs, grouped by MedDRA body system and PT, will be summarized by dose groups. In general, tables will have events categorized into all TEAEs and treatment-related TEAEs.

Multiple occurrences of the same AE (at the PT level) in the same subject will be counted only once in the frequency tables. If a subject experiences multiple episodes of the same event with different relationship/severity, the event with the strongest relationship or maximum severity to study drug will be used to summarize AEs by relationship and severity.

The following summary tables will be produced:

1. Treatment emergent adverse events
2. Treatment emergent adverse events by severity
3. Treatment related treatment emergent adverse events
4. Treatment related treatment emergent adverse events by severity
5. Serious adverse events

Additionally, all SAEs, regardless of their treatment-emergent status will be summarized by SOC and PT.

The following listings will be produced

1) All TEAEs
2) AEs leading to discontinuation
3) SAEs

4.9.7.2. Laboratory Measurements

Descriptive statistics for continuous hematology, clinical chemistry, urinalysis, and coagulation laboratory measurements will be generated. Raw data and change from baseline in clinical laboratory parameters will be summarized by dose group. Shift tables comparing N (%) of low, normal and high status of the lab values from Baseline to each time point will be produced. A table of frequencies of predefined change abnormal (PCA) increases and PCA decreases as defined in tables 4.9.7.2-1, 4.9.7.2-2, and 4.9.7.2-3, will be generated by time point. Laboratory data will be presented in the data listings showing all predefined change (PC) values, as appropriate.

Changes in renal function tests will be produced. At each time point, the number and percentage of subjects in each cohort with Grade 1, Grade 2, Grade 3, or Grade 4 toxicity serum creatinine levels will be presented. In addition, the number of percentage of subjects who meet the following criteria will be provided:

- A $\geq$ 1.5-fold increase in serum creatinine level from baseline.
- A decrease in GFR to < 70 mL/min.
- A > 3-fold increase in urine albumin creatinine ratio from baseline to an absolute value of > 30 mg/g.
- A > 30% increase in serum cystatin C from baseline to a level above the normal reference range.

Table 4.9.7.2-1 Predefined Changes in Hematology Laboratory Values

Test	Unit	Predefined Change*		Clinically noteworthy criteria
		Decrease	Increase	
Hematocrit	1	0.07		Simultaneous TEMAs with hemoglobin and value < 0.33%
Hemoglobin	g/L (or mmol/L)	19.3 (or 1.2)		Simultaneous TEMAs with hematocrit and value < 110 g/L (< 6.8 mmol/L)
Red blood cell count	T/L	0.7		
Mean corpuscular volume (MCV)	FL	9	8	
Mean corpuscular hemoglobin (MCH)	Pg	3.06	3.22	
Mean corpuscular hemoglobin conc. (MCHC)	mmol/L	2	2	
White blood cell count	count/L	1.0	3.7	TEMA and value < 0.75×LLN or TEMA and value > 1.5×ULN
Platelet count	count/L	93	107	TEMA and value <100 G/L
Basophils (abs)	count/L	(0.13)	0.13	
Eosinophils (abs)	count/L	(0.38)	0.37	
Lymphocytes (abs)	count/L	0.35	1.54	
Monocytes (abs)	count/L	(0.44)	0.46	
Neutrophils (abs)	count/L	0.60	3.18	

- *Values in parentheses indicate that changes in the given direction are generally not relevant.
- TEMA = treatment emergent markedly abnormal
- ULN= upper limit of normal
- LLN = lower limit of normal

Table 4.9.7.2-2 Predefined Changes in Chemistry Laboratory Values

Test	Unit	Predefined Change		Clinically noteworthy criteria
		Decrease	Increase	
Fasting blood glucose*	mmol/L	3.1	3.2	
Urea (BUN)	mmol/L		3.2	TEMA and value>1.5×ULN
Creatinine	μmol/L		35	TEMA and value>1.5×ULN
Sodium	mmol/L	8	8	
Potassium	mmol/L	1.1	1.0	Value > 5.5 mmol/L
Chloride	mmol/L	9	8	
Uric acid	μmol/L		119	
Calcium[#]	mmol/L	0.30	0.30	
Total cholesterol	mmol/L		1.73	
AST (SGOT)	U/L		22	Value > 3×ULN
ALT (SGPT)	U/L		28	Value > 3×ULN
Gamma GT	U/L		29	Value > 3×ULN
Alkaline phosphatase	U/L		28	Value > 1.5×ULN
Total protein[@]	g/L	11	10	
Albumin	g/L	7	6	
Total bilirubin[&]	μmol/L		10	Value > 1.5×ULN
Creatine phosphokinase	U/L		236	Value ≥ 2× Baseline Value
Inorganic phosphorus	mmol/L	0.45	0.42	
Triglycerides	mmol/L		2.88	

*Convert to SI unit by multiplying mg/dL value by 0.0555; [#]multiply mg/dL value by 0.25;[@]multiply g/dL value by 10; [&]multiply mg/dL value by 17.1;
TEMA = treatment emergent markedly abnormal
ULN= upper limit of normal

Table 4.9.7.2-3 Predefined Changes in Urinalysis Laboratory Values

Test	Predefined Change		Clinically noteworthy criteria
	Decrease	Increase	
pH	2.0	2.0	
Specific gravity	0.018	0.017	
Creatinine			Value > 3X Baseline Value to an absolute value >30 mg/g.

4.9.7.3. Vital Signs

Descriptive statistics for vital signs parameters will be generated. Vital signs data will be presented in the data listings showing all PC values, as appropriate.

Additionally, the following will be provided:

- A table of descriptive statistics of the vital sign parameters will be given for Baseline, each time point, and for the change from Baseline to each time point.
- A table of frequencies of PCA and last predefined change abnormal (LPCA) increases and decreases, as defined in table 4.9.7.3-1, by time point.

Table 4.9.7.3-1 Predefined Changes in Vital Signs

Variable	Units	Lower limit of normal	Upper limit of normal	Predefined decrease	Predefined increase
Systolic blood pressure	mm Hg	90	140	≥30	≥30
Diastolic blood pressure	mm Hg	50	90	≥20	≥20
Pulse	beats/min	55	100	≥20	≥20
Respiration	breaths/min	12	20	≥10	≥10
Temperature	ºC	36	38	–	–

4.9.7.4. 12-Lead ECGs

Descriptive statistics for ECG parameter will be generated. ECG data will be provided in a listing showing all PC values, as appropriate.

Specifically, the following will be provided:

- A table of descriptive statistics of the ECG parameters will be given for Baseline, each time point, and for the change from Baseline at Day 14.
- A shift table will compare N (%) of ECG status at Baseline to Day 14.
- A table of frequencies of PCA and LPCA increases and decreases, as defined in table 4.9.7.4-1, by time point.

Table 4.9.7.4-1 Predefined Changes in 12-Lead ECG

Variable	Units	Lower limit of normal	Upper limit of normal	Predefined decrease	Predefined increase
Heart rate	beats/min	55	100	≥20	≥20
QTc interval (male)	ms	–	440	–	30-59, ≥60
QTc interval (female)	ms	–	460	–	30-59, ≥60
QRS interval	ms	–	120	–	≥10
PR interval	ms	–	200	–	≥20

4.9.7.5. Physical Examinations

The physical examination results will be listed by subject in a data listing.

4.9.7.6. Pharmacokinetic Analysis

The details of the PK analysis will be outlined in a separate PK analysis plan.