RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-ASCENDING DOSE STUDY TO DETERMINE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF UV-4B SOLUTION ADMINISTERED ORALLY IN HEALTHY SUBJECTS

DMID Protocol Number: DMID 15-0062

DMID Funding Mechanism: HHSN272201100030C

Contract Research Organization: [redacted]

IND Sponsor: Emergent Product Development Gaithersburg, Inc.
300 Professional Drive
Gaithersburg, MD 20879

Principal Investigator(s): [redacted]

Emergent Product Development Gaithersburg, Inc. Medical Monitor: [redacted]

DMID Medical Monitor: [redacted]

Immediately Reportable Serious Event(s): Emergent Global Pharmacovigilance Department [redacted]

Version Number: 4.0

Date: 10 January 2017

Statement of Compliance

The study will be carried out in accordance with ethical principles that have their origin in The Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 11, and 21 CFR Part 312)
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997)
- National Institutes of Health (NIH) Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subject's Protection Training.

Sponsor Signature Page

Protocol Title:	Randomized, Double-blind, Placebo controlled, Multiple-Ascending Dose Study to Determine the Safety, Tolerability and Pharmacokinetics of UV-4B Solution Administered Orally in Healthy Subjects
Protocol Number:	DMID 15-0062
Protocol Version (Issue Date):	4.0 (10 January 2017)

INVESTIGATOR SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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Table of Contents

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List of Abbreviations

° C	Degrees in Celsius
° F	Degrees in Fahrenheit
ABCDE	Airway, Breathing, Circulation, Disability, and Exposure
AE	Adverse event/Adverse experience
A_e	Amount of analyte excreted
ALS	Advanced life support
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{(0\text{-}inf)}$	Area under plasma concentration-time curve from time zero extrapolated to infinity
$AUC_{(0\text{-}last)}$	Area under plasma concentration-time curve from time zero to time of last quantifiable analyte concentration
$AUC_{(0\text{-}8)}$	Area under plasma concentration-time curve from time zero to 8 hours post-dose
$AUC_{(0\text{-}24)}$	Area under plasma concentration-time curve from time zero to 24 hours post-dose
BID	Twice daily
BL	Baseline
BMI	Body mass index
Bpm	Beats per minute
BSA	Body surface area
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
cGMP	Current good manufacturing practice
CPK	Creatine phosphokinase
CL/F	Apparent systemic clearance
CL_r	Renal clearance
C_{max}	Observed maximum plasma concentration
CNS	Central nervous system
CO2	Carbon dioxide
CQMP	Clinical Quality Management Plan
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract Research Organization
CROMS	Clinical Research Operations and Management Support

CRU	Clinical Research Unit
$C_{ss\ (trough)}$	Trough concentration at steady state, observed or calculated
CV	Cardiovascular
CYP	Cytochrome P450
DENV	Dengue virus
DHHS	Department of Health and Human Services
dL	Deciliter
DMID	Division of Microbiology and Infectious Diseases
DNJ	1-deoxynojirimycin
DBP	Diastolic blood pressure
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic data capture
ER	Endoplasmic reticulum
FDA	Food and Drug Administration
FOB	Functional Observational Battery
FOS	Cytosolic free oligosaccharides
f_e	Fraction of analyte excreted
FSH	Follicle-stimulating hormone
G	Grams
GALT	Gut-associated lymphoid tissue
GCP	Good Clinical Practice
GGT	γ-Glutamyltransferase
GI	Gastrointestinal
Glc	Glucose
GLP	Good Laboratory Practice
H	Hour
HCG	Human chorionic gonadotropin
HCl	Hydrochloride
HCT	Hematocrit
HDPE	High-density polyethylene
HED	Human-equivalent dose
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
Hpf	High powered field
HS	Hypersensitivity

IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug Application
IP	Investigational Product
INR	International normalized ratio
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IV	Intravenous
K_a	First order absorption rate constant
Kg	Kilogram
Lck	Lymphocyte-specific protein tyrosine kinase
LDH	Lactate dehydrogenase
LFT	Liver function test
µg	Microgram
µM	Micromolar
M	Meter
MAD	Multiple-ascending dose
Max	Maximum
MCV	Mean corpuscular volume
MED	Minimal effective dose
MedDRA®	Medical Dictionary for Regulatory Activities
MDCK	Madin-Darby canine kidney
mEq	Milliequivalents
Mg	Milligram
Min	Minutes
mL	Milliliter
mmHg	Millimeters of Mercury
MOA	Mechanism of action
Ms	Millisecond
MTTD	Mean time to death
N	Number (typically refers to subjects)
Ng	Nanogram
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health

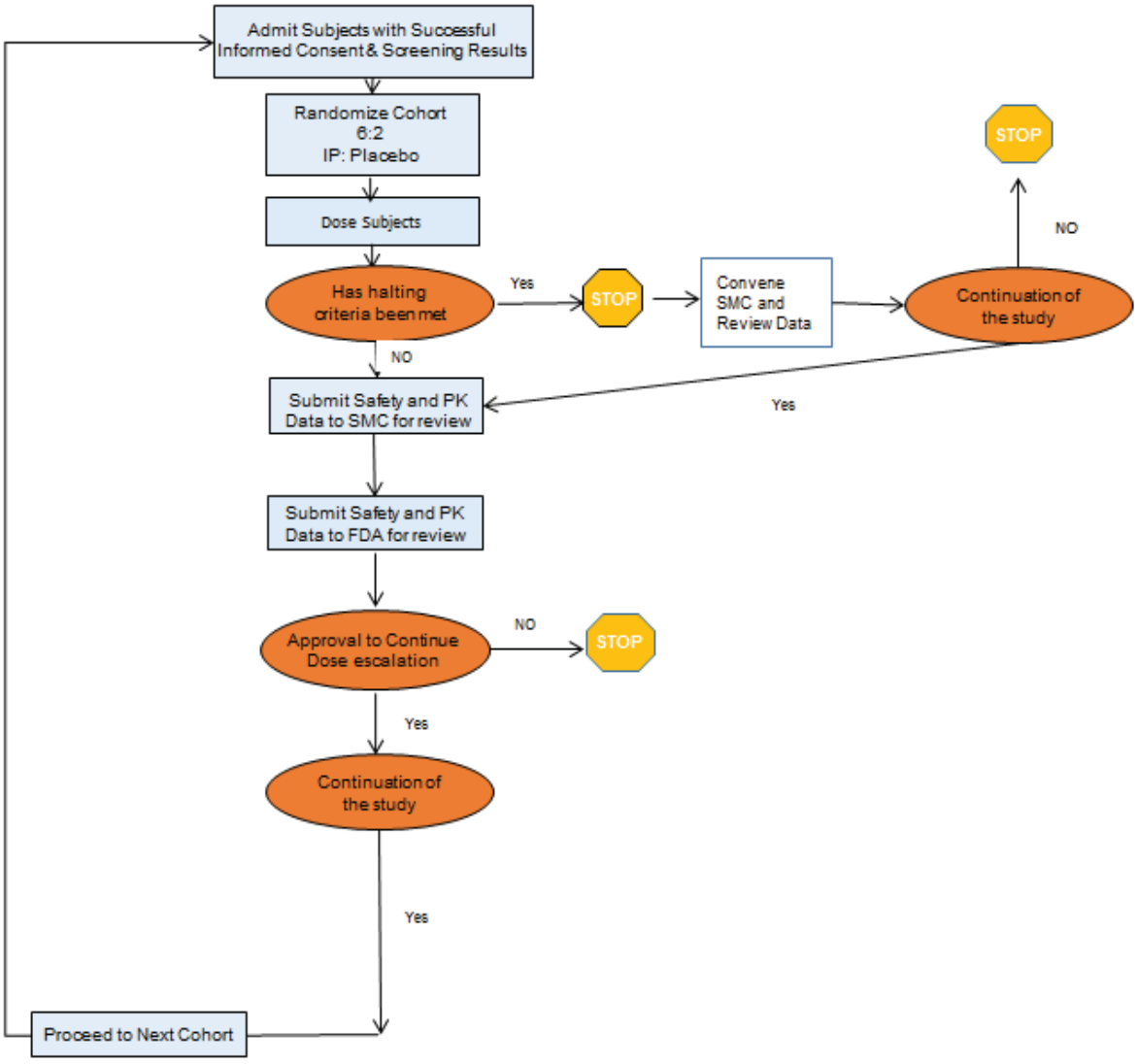
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NPC	Niemann-Pick disease
OPA	Oropharyngeal Airway
pH	A measure of the acidity or alkalinity of a solution
PI	Principal Investigator
PK	Pharmacokinetics
PLT	Platelet
PT	Prothrombin time
PVG	Pharmacovigilance
QD	Once daily
QRS	Combination name of three graphical deflections on ECG
QT	Total cardiac output
QTc	Heart rate-corrected QT interval
QTcF	Fridericia's corrected QT interval
RBC	Red blood cells
SAD	Single-ascending dose
SAE	Serious Adverse Event/Serious Adverse Experience
SBP	Systolic blood pressure
SD	Standard deviation
SMC	Safety Monitoring Committee
SOP	Standard operating procedure
TID	Three times a day
$t_{1/2}$	Terminal half life
λ_z	Terminal rate constant
t_{max}	Time to reach maximum plasma concentration
ULN	Upper limit of the normal range
US	United States
V_z/F	Apparent volume of distribution during the terminal phase (extravascular)
WBC	White blood cells
WFI	Water for irrigation
WHO DD	World Health Organization Drug Dictionary

Protocol Summary

Title:	RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-ASCENDING DOSE STUDY TO DETERMINE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF UV-4B SOLUTION ADMINISTERED ORALLY IN HEALTHY SUBJECTS
Phase:	1B
Protocol Number	DMID 15-0062
Population:	Healthy male and female subjects between the ages of 18 and 45 years inclusive, with a body mass index (BMI) between 18 and 32 kg/m^2 inclusive, and a minimum body weight of 60 kg and maximum body weight of 90 kg, will be enrolled (up to 5 cohorts)
Number of Sites:	Up to two Phase 1 study sites
Study Duration:	Approximately 12 months
Number of Subjects	Approximately 40
Subject Participation Duration:	Approximately 5 to 6 weeks: There will be an up to 21-day screening period, followed by 1 residential period from the day before dosing (Day -1) until discharge on Day 8. There will be follow up visits on Day 10±1 and Day 15 ±1.
Description of Product:	UV-4B (hydrochloride [HCl]) salt of UV-4) oral solution, 30 mg to 150 mg of free base, 30mL including 10mL OraSweet SF taste masking solution. UV-4B clinical trial material is drug substance packaged in double polypropylene bags in HDPE containers and stored at 2-8°C. At time of use, bulk drug substance will be solubilized in water for irrigation. UV-4B stock solution will be transferred into an oral dosing container, 10 mL of taste-masking agent added, and volume adjusted to 30 mL.
Description of Placebo:	Placebo oral solution (10mL OraSweet SF diluted with water)
Objectives:	Primary: To evaluate the safety and tolerability of UV-4B given three times a day (TID) for up to 7 days in healthy subjects. Secondary: To determine pharmacokinetic parameters describing absorption and clearance of UV-4B given TID for 7 days in healthy subjects.
Description of Study Design:	This is a multiple-ascending dose (MAD) study with up to five cohorts of healthy subjects planned. Each cohort will consist of 8 subjects (6 active; 2 placebo). Within each cohort, subjects will be randomized to receive UV-4B oral solution or placebo solution TID (every 8 hours ± 0.5) for 7 days. A Safety Monitoring Committee (SMC) review of all safety and tolerability data will be conducted after completion of each cohort. The SMC will also be consulted for any specific safety signals at any point during the study, to include dose-related trends within the normal range. The SMC will review all safety and PK data after completion of each cohort. Upon completion of review by the SMC, safety summary and PK data will be sent to the Food

	and Drug Administration (FDA), for review. The study will be paused during FDA review and dose escalation will only proceed upon approval by the FDA. A protocol amendment for further dose escalations (Cohorts 4 and 5), if appropriate, will be submitted to DMID, the SMC and the FDA for review after Cohort 3. In accordance with DMID stated policy, Emergent Product Development Gaithersburg, Inc. (Emergent) will allow for a 30-day FDA review of any such protocol amendment. Safety assessments will include telemetry, 12-lead electrocardiogram (ECG) measurements, vital signs, physical examinations, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, vomitus occult blood and fecal occult blood), and adverse events (AEs). Blood samples will be collected for pharmacokinetics at multiple time points until discharge. Plasma will be tested to determine the following parameters for UV-4B in subjects: UV-4 plasma concentrations and pharmacokinetic (PK) parameters determined on day 1 (after first dose up to second dose) and after last dose on Day 7 Maximum plasma concentration [C_{max}] Time to reach maximum plasma concentration [t_{max}] Area under the plasma concentration curve from time zero extrapolated to last quantifiable concentration [$AUC_{(0\text{-}last)}$] (after first dose report $AUC_{(0\text{-}8)}$), Total daily exposure ($AUC_{(0\text{-}24)}$) AUC from time zero extrapolated to infinity [$AUC_{(0\text{-}inf)}$] (Day 7 only), Systemic clearance [CL/F] Volume of distribution [V_z/F], Terminal half-life [$t_{1/2}$] (after last dose), Accumulation ratio as defined by $AUC_{(0\text{-}8)}$ after the last dose divided by $AUC_{(0\text{-}8)}$ after the first dose, The results of these preliminary safety and PK results will be listed and summarized to assist in future dose calculations.
Estimated Time to Complete Enrollment:	Approximately 10 months

Schematic of Study Design



Continuation of study will be upon FDA approval only

1 KEY ROLES

Individuals:

Principal Investigators:

[redacted]

Emergent Medical Monitor: [redacted]

Emergent Clinical Project Specialist: [redacted]

Division of Microbiology and Infectious Diseases (DMID)

DMID Medical Officer: [redacted]

DMID Medical Monitor: [redacted]

Clinical Project Manager: [redacted]

Pharmacovigilance:
Emergent Global Pharmacovigilance Department
[redacted]

Data Management:
[redacted]

[redacted]

Clinical Laboratories:

[redacted]

[redacted]

Bioanalytical Laboratory:

[redacted]

Dose Confirmation Analytical Laboratory:

[redacted]

Investigator Sites:

[redacted]

[redacted]

[redacted]

Institutional Review Board:

[redacted]

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Pharmacology

[redacted]

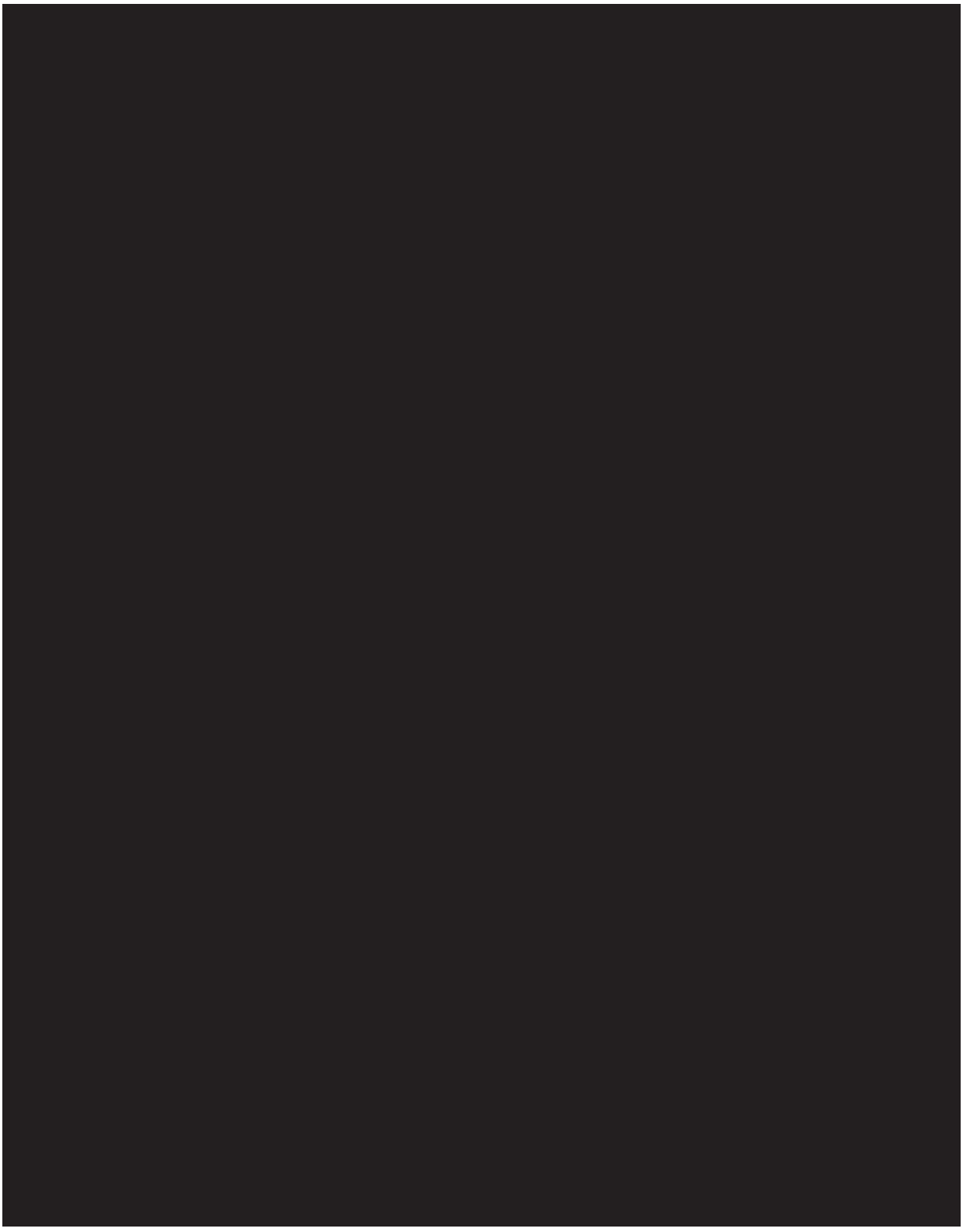
2.1.2 Nonclinical Absorption, Distribution, Metabolism, Excretion, and Pharmacokinetics

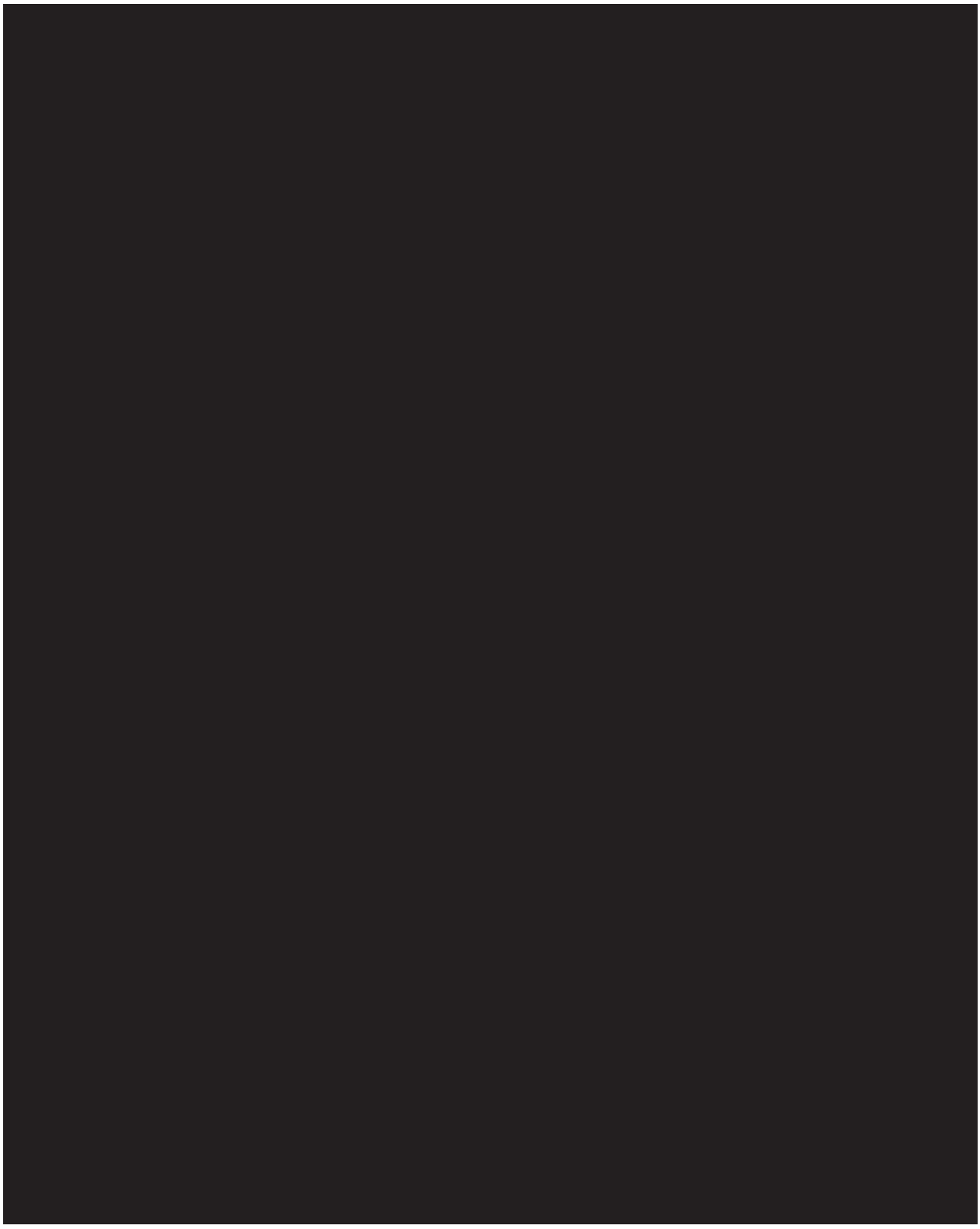
[redacted]

[redacted]

2.1.3 Safety Pharmacology and Toxicology

[redacted]





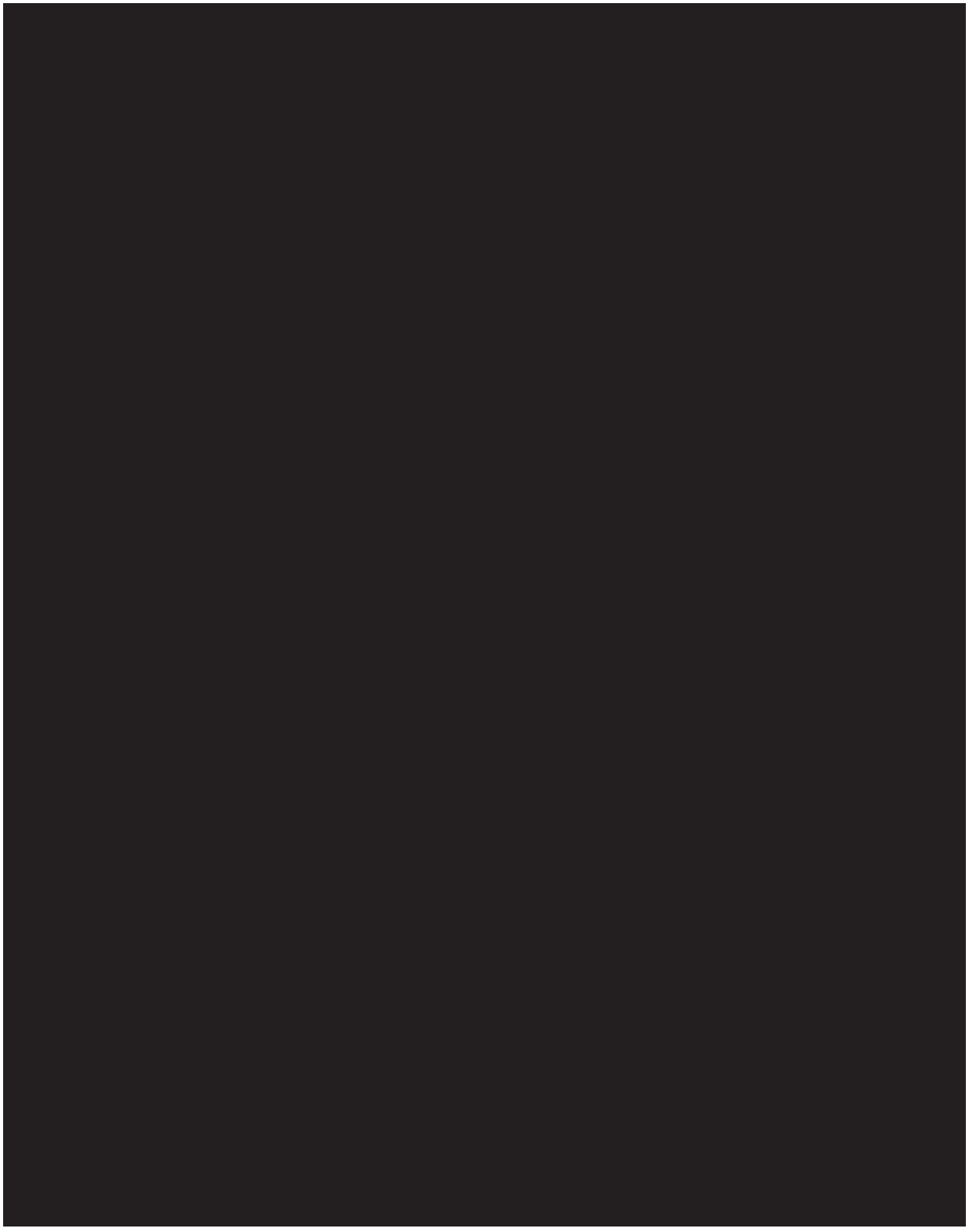
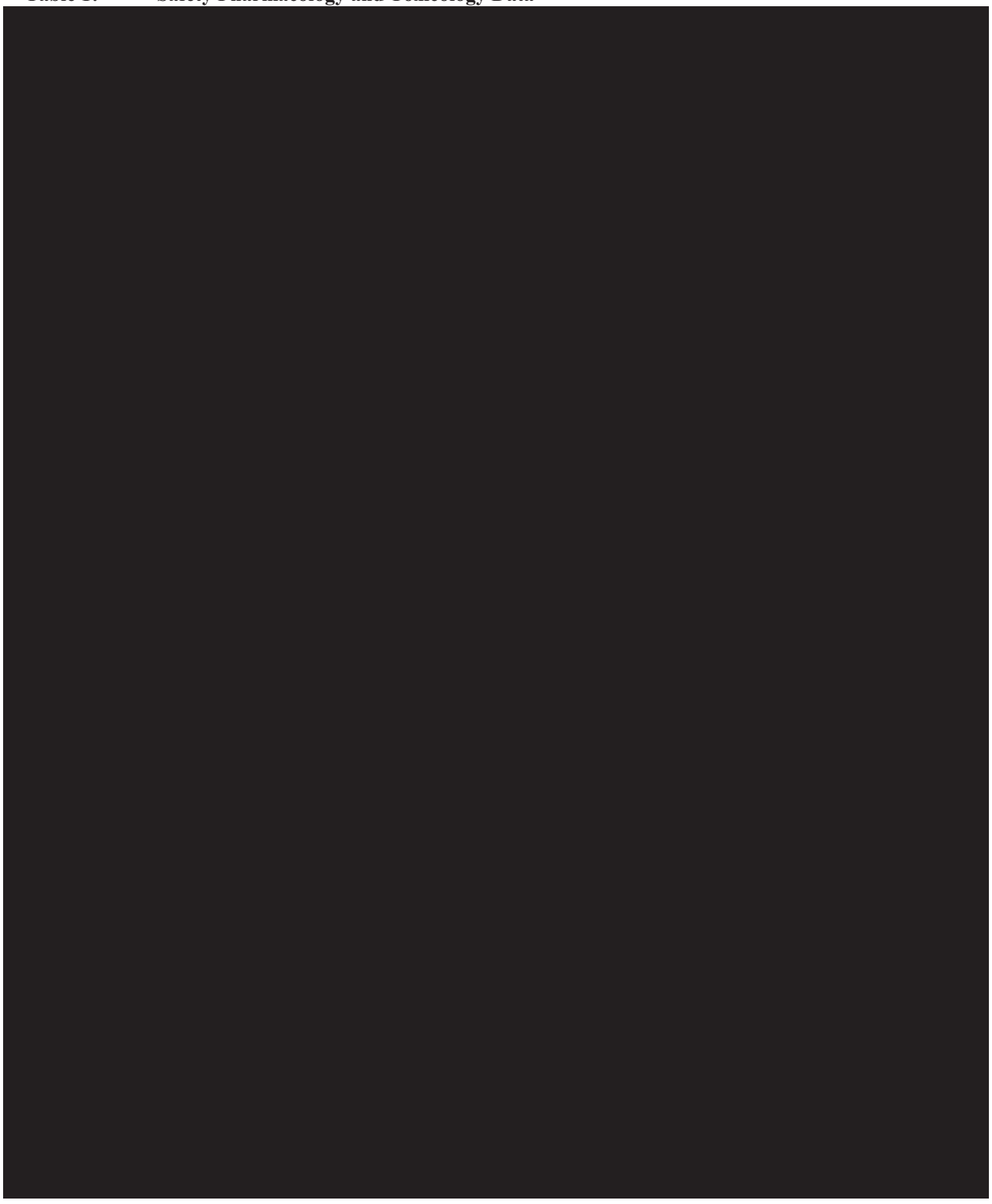
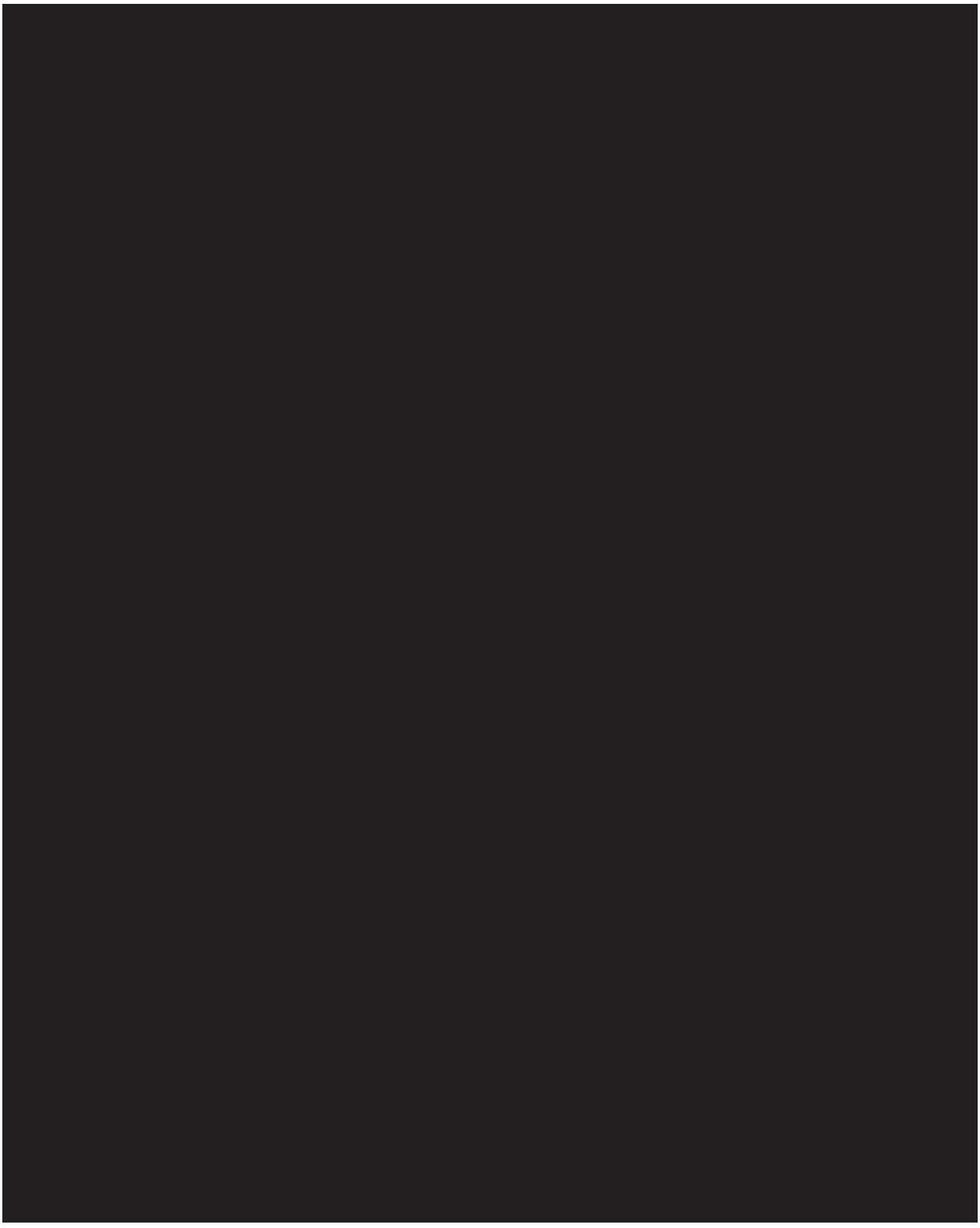
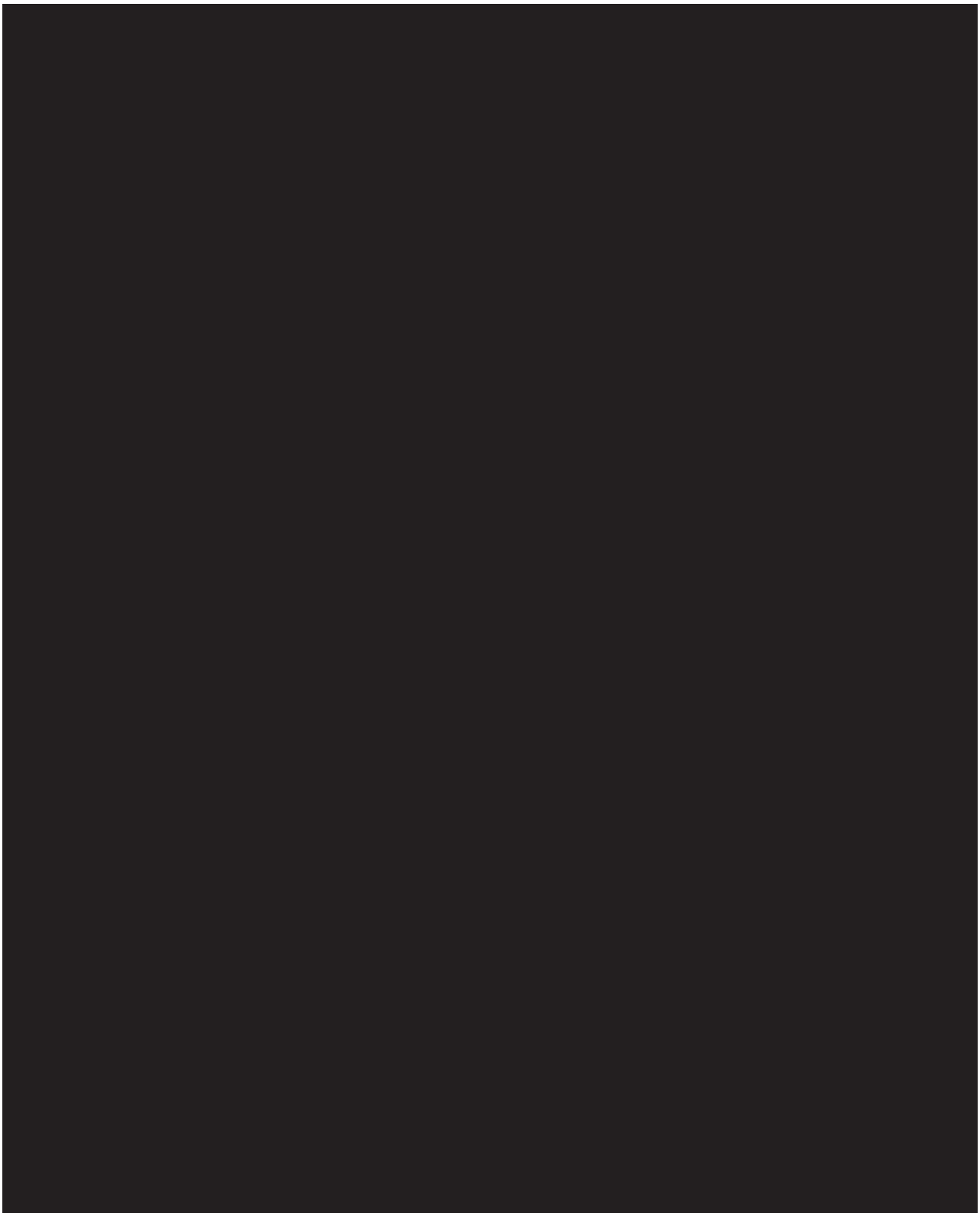
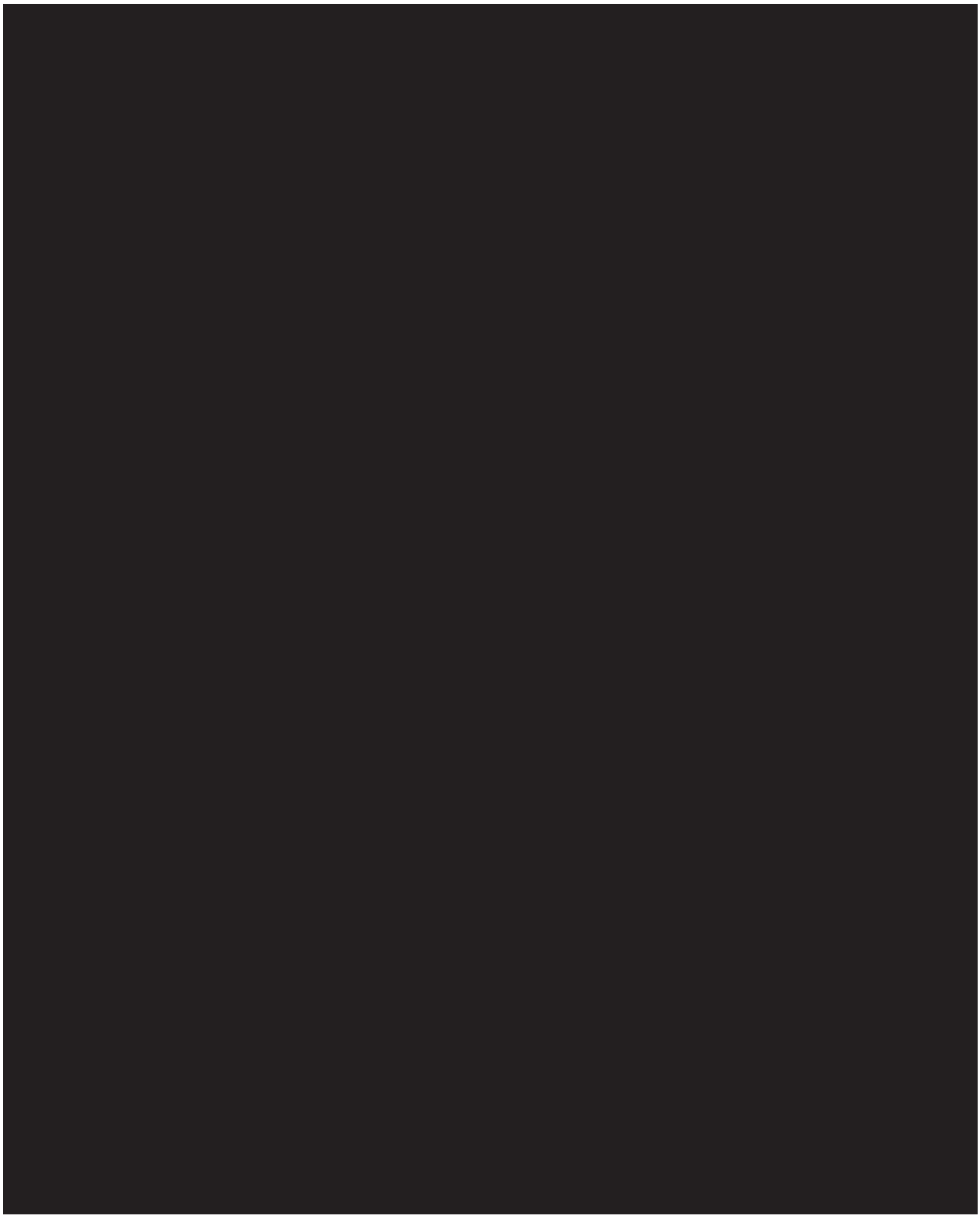


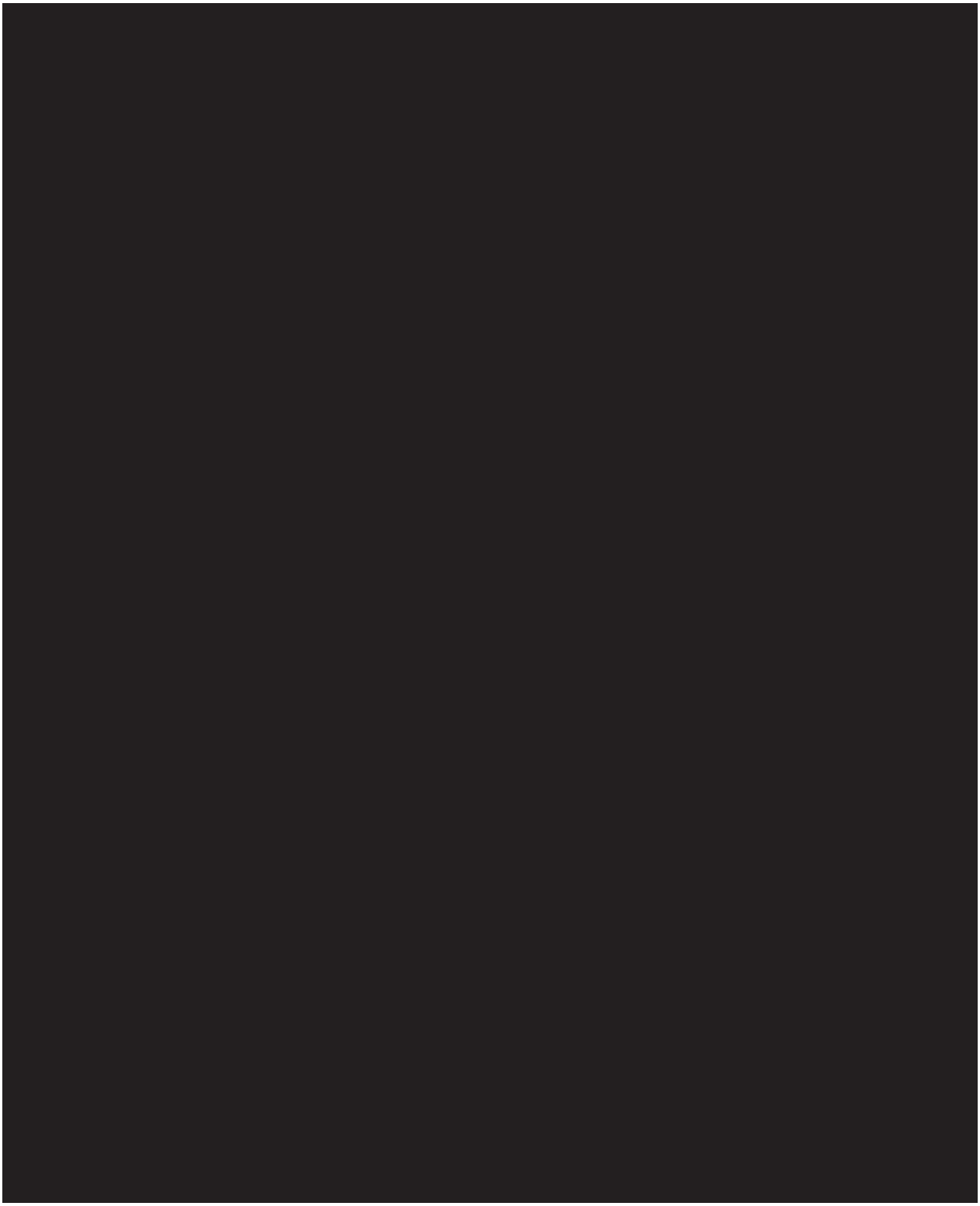
Table 1: Safety Pharmacology and Toxicology Data

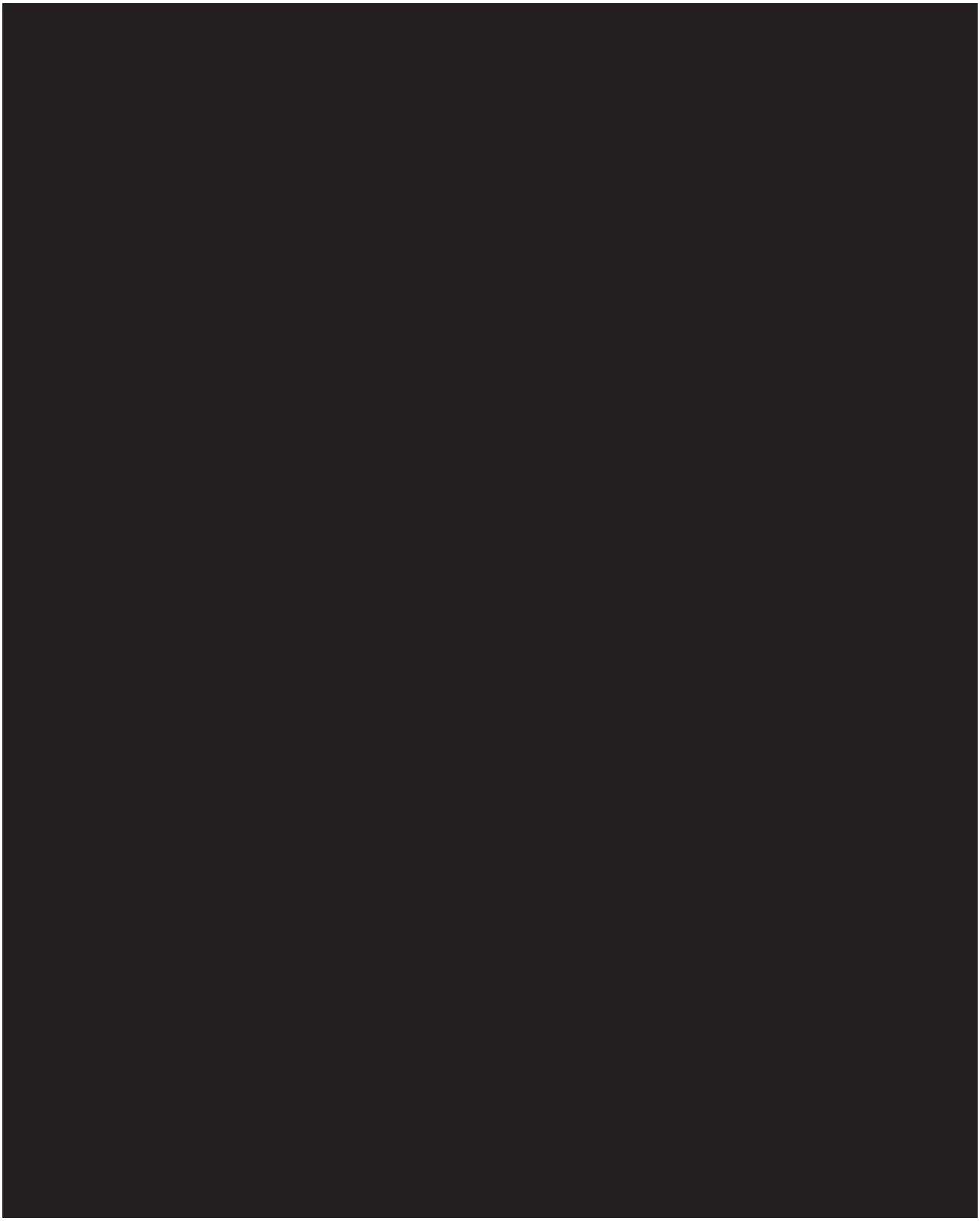












[redacted]

2.1.4 Clinical Pharmacokinetic data

[redacted]

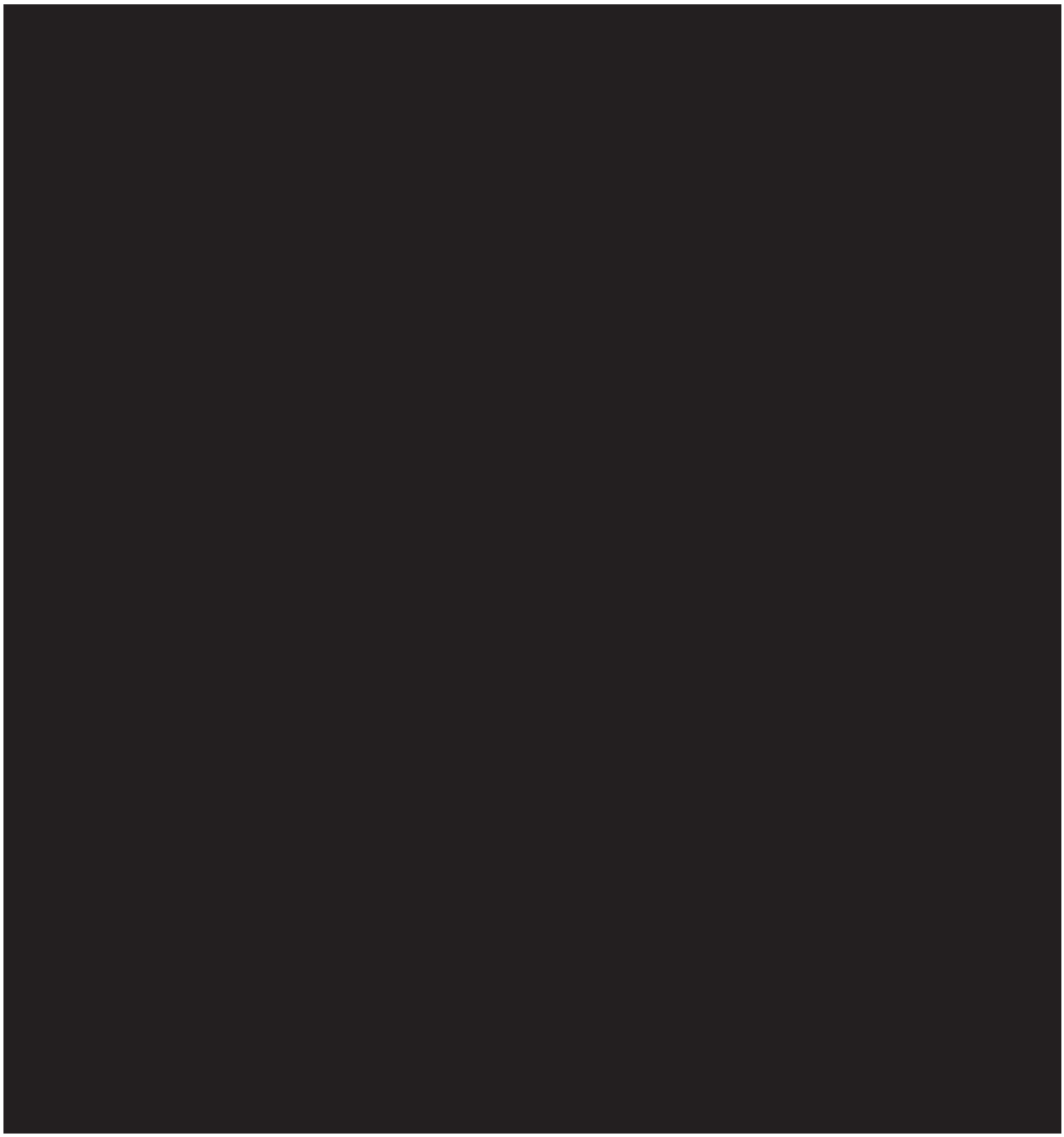
[redacted]

2.1.5 Clinical Safety data

[redacted]

2.2 Rationale for Dose Selection

[redacted]



Dose escalation will proceed as shown in Table 2 below.

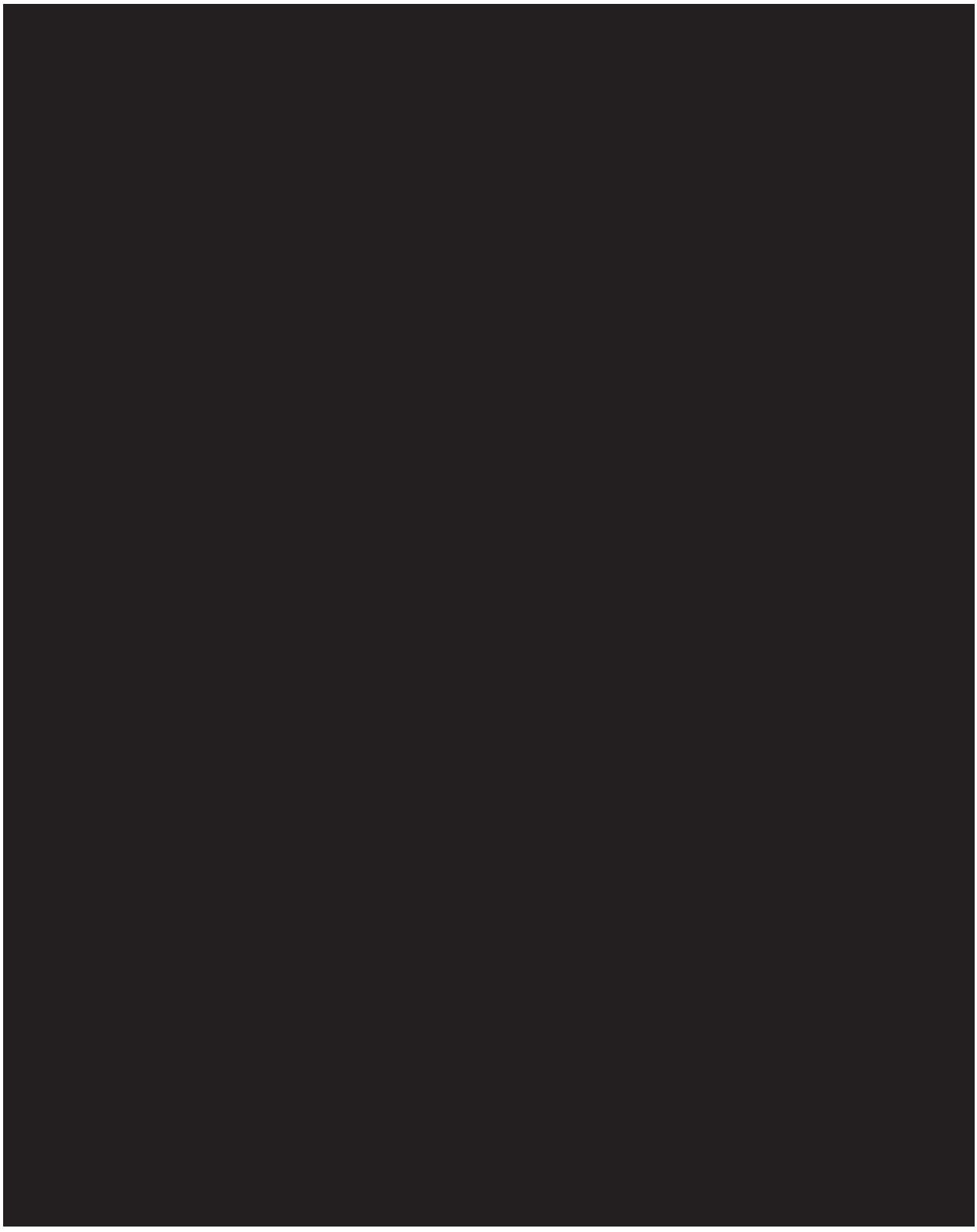
Table 2: Proposed Dose Escalation

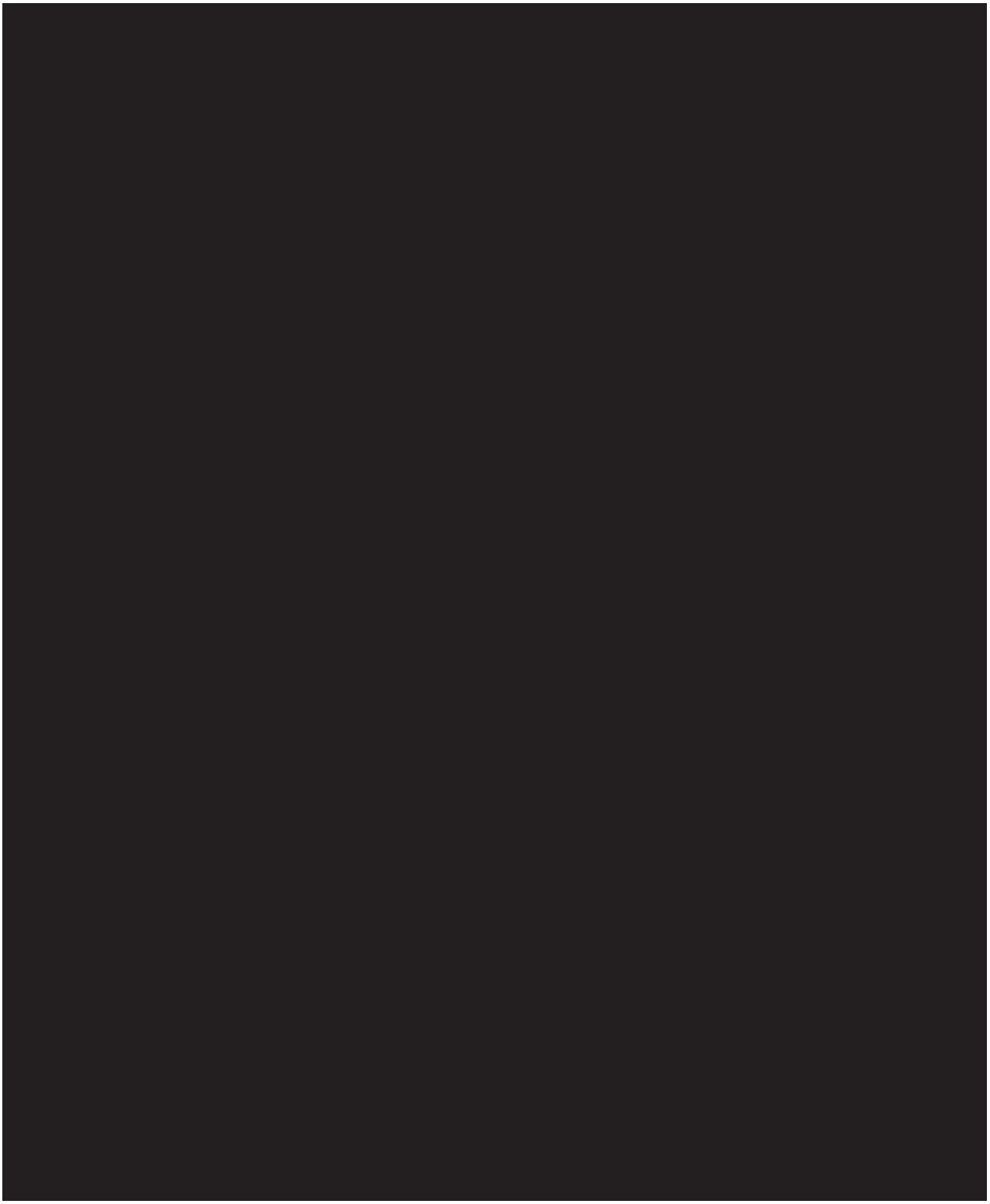
Cohort	Proposed Dose Escalation Scheme	Dose (mg) TID
1	Starting dose	30
SMC and FDA review of Safety and PK Data		
2	Increase 2.5x	75
SMC and FDA review of Safety and PK Data		
3	Increase 2x	150
SMC and FDA review of all Safety and PK Data and Protocol Amendment		
4	TBD	TBD
5	TBD	TBD

Table 3: Planned MAD Doses and Calculated Safety Margins (3 cohorts)

2.3 Potential Risks and Benefits

2.3.1 Potential Risks





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2.3.2 Known Potential Benefits

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3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of UV-4B given TID for 7 days in healthy subjects.

3.1.2 Secondary Objective

The secondary objective of the study is to determine PK parameters describing absorption and clearance of UV-4B given TID for 7 days in healthy subjects.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

- Evaluation and occurrence of AEs and serious adverse events (SAEs)
- Determination of changes from baseline for clinical laboratory tests

3.2.2 Secondary Outcome Measures

- Determination of changes from baseline for PE, vital signs, and ECGs
- UV-4 plasma concentrations and PK parameters [including C_{max}, t_{max}, $AUC_{(0\text{-}last)}$,
- $AUC_{(0\text{-}8)}$ $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}inf)}$, CL/F, V_z/F, $t_{1/2}$, and accumulation ratio as defined by $AUC_{(0\text{-}8)}$ after the last dose divided by $AUC_{(0\text{-}8)}$ after the first dose]

4 STUDY DESIGN

This is a MAD study with up to five cohorts of healthy subjects planned (18-45 years inclusive) (Table 2). Each cohort will consist of 8 subjects (6 active; 2 placebo). Within each cohort, subjects will be randomized to receive UV-4B oral solution or placebo TID for 7 days (every 8 hours ± 0.5 hours). The study product and placebo will be masked so that the subjects and the site personnel including the PI will be blinded to the treatment assignment. Recruitment will occur at up to two investigational sites.

Safety assessments will include telemetry, 12-lead ECG measurements, vital signs, physical examinations, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, vomitus occult blood and fecal occult blood), and AEs. Subjects will return to the clinic on Day 10 (±1) for additional safety assessments and blood draws for laboratory assessments and on Day 15 (±1) for the final study follow-up visit.

The SMC will review all safety and PK data after completion of each cohort. Upon completion of review by the SMC, safety summary and PK data will be sent to the Food and Drug Administration (FDA), for review. The study will be paused during review. Upon FDA approval, the next cohort will be dosed according to the dose escalation outlined in Table 2, unless otherwise modified by the FDA. Upon completion of dosing in the third cohort, safety and PK data and a draft protocol amendment (Cohorts 4 and 5) will be submitted for SMC review. In addition, the cumulative safety and PK summary, minutes and recommendations from the SMC meeting, and the SMC reviewed protocol amendment for Cohorts 4 and 5 will be submitted to the FDA for review. In accordance with DMID stated policy, Emergent will allow for a 30-day FDA review of the protocol amendment.

5 STUDY ENROLLMENT AND WITHDRAWAL

Only subjects who meet all of the inclusion and none of the exclusion criteria prior to dosing will be eligible for enrollment into this study. No exemptions are granted on inclusion/exclusion criteria in DMID-sponsored studies.

Subjects who are screen failures due to transient conditions are permitted to be rescreened one time. In the event that the subject is rescreened for trial participation, a new informed consent form (ICF) must be signed.

5.1 Subject Inclusion Criteria

Subjects may be entered in the study only if all of the following criteria are met:

1. Capable of understanding and complying with the requirements of the study and have signed the Informed Consent Form (ICF);
2. Healthy male and female subjects between 18 and 45 years of age, inclusive;
3. Females must have negative serum and urine pregnancy tests at screening and on admission to the unit, and must not be lactating, confirmed at screening and at check-in;
4. Females must meet one of the following criteria at screening:
   - Confirmed to be post-menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone (FSH) levels in the laboratory-defined postmenopausal range or;
   - Have documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or tubal ligation or occlusion or;
   - If of child bearing potential (does not meet the criteria stated above), starting at least 14 days prior to the first dose of study product and continuing for at least 3 months after the last dose, willing to use:
     a. hormonal contraception plus barrier contraception (condom or occlusive cap such as a diaphragm or surgical vault cap) AND spermicidal foam/gel/cream/suppository or;
     b. intrauterine device plus barrier contraception (condom or occlusive cap such as a diaphragm or surgical vault cap) AND spermicidal foam/gel/cream/suppository;
5. BMI between 18 and 32 kg/m^2, inclusive;
6. Minimum body weight of 60 kg;
7. Maximum body weight of 90 kg;

8. Healthy male subjects must agree to not donate sperm from the first day of dosing until 3 months after the last dose of UV-4B and be willing to use barrier contraception during sexual intercourse, e.g., condoms, even if they have had a vasectomy, their partners are postmenopausal, surgically sterile, or are using accepted contraceptive methods as defined in inclusion criterion 4 above, from the first day of dosing until 3 months after the last dose of UV-4B;
9. Willing to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation: Strenuous exercise (i.e. long distance running > 5km/day, weight lifting, or any physical activity to which the subject is not accustomed) is to be avoided starting 96 hours (4 days) prior to dosing on Day 1 through the period of confinement in the Clinical Unit and for at least 96 hours prior to the follow-up visits;
10. Nonsmokers (refrained from any tobacco usage, including smokeless tobacco, nicotine patches, etc., for 3 month prior to the administration of the study product); subjects must have a negative test result for cotinine.

5.2 Subject Exclusion Criteria

Subjects presenting with any of the following must not be included into the study:

1. History of allergy to drug in the iminosugar class;
2. Treatment with any investigational products or therapies within 30 days (or 5 half-lives, whichever is greater) prior to the first day of dosing;
3. Currently has, or has a history of, disease or dysfunction of the pulmonary, cardiovascular, endocrine, hematologic, neurological, immune, GI, genitourinary, or other body system, that is likely to affect the safety of the subject;
4. Creatinine clearance < 90 mL/min (based on Cockcroft-Gault equation);
5. Proteinuria greater than or equal to 1+;
6. At screening, Grade 1 or higher abnormalities in supine vital signs to include deviations in temperature, resting heart rate, blood pressure, and respiratory rate (may be repeated once); at check-in (Day -1), Grade 2 or higher abnormalities in supine vital signs (see Appendix II). A second set of values were added to the toxicity table for subjects who present with asymptomatic bradycardia at baseline at time of screening (<60 bpm);
7. Abnormalities of physical exam suggestive of conditions that would pose an increased risk to the subject;
8. Abnormal ECGs; however, abnormal readings for the following benign conditions will be acceptable for the study: sinus bradycardia, sinus arrhythmia, early repolarization, nonspecific ST-T wave pattern or changes, right axis deviation (axis 100 degrees or less), first degree AV block (PR interval less than 210ms), nonspecific intraventricular

conduction delay (QRS less than 120ms), indeterminate axis, and short PR interval (where no delta wave).

If an abnormal ECG finding is previously recorded, medically insignificant, and attributed to other causes (i.e. body habitus), Principal Investigator (PI) may elect to enroll the subject.

9. At screening, laboratory values outside of the normal range; however, the following list of parameters (see below table) are not considered exclusionary if values fall outside of the normal range. At baseline/check-in (Day -1), values that are Grade 2 or higher based on the toxicity grading scale (Appendix II).

Low Chemistry Values	High Chemistry Values	Urinalysis	Hematology Values	Low Coagulation Values
Alkaline Phosphatase AST ALT GGT LDH Creatinine Phosphorus Bicarbonate Uric Acid CPK Chloride BUN Bilirubin (total, indirect, direct) Lipase Amylase	Chloride CPK less than 400 (CO2)	High or low specific gravity High or Low pH Trace protein, when specific gravity is higher than 1.015 Mucus Crystals Ketones when blood sugar is normal Hyaline casts Blood (unless greater than 3 RBC/hpf and or CPK greater than 400) Epithelial Cells Bacteria < many *Urine Spermatozoa	Low-Basophils Low-Eosinophils Lymphocytes Monocytes Neutrophils Differential percentages, absolute values and RBC indices	PT aPTT
*when urine spermatozoa are present, urine protein must be repeated if result is elevated.				

10. Any known or expected risk of bleeding, such as, but not limited to:

- laboratory evidence of active bleeding, such as positive fecal occult blood, or positive urinary blood that is greater than 3 RBC/hpf (Day 1 except women who are menstruating);
- history of peptic ulcer, GI bleeding (including hematemesis, melena, bloody emesis or rectal bleeding) or bleeding from hemorrhoids;

- history of minor bleeding episodes such as, rectal bleeding (spots of blood on toilet paper), and gingival bleeding within 3 months before the first dose;
- any family history (suspected or documented) of coagulopathy;
- females with a history of dysfunctional uterine bleeding, including history of menorrhagia (heavy menstrual bleeding), metrorrhagia, or polymenorrhea;
- use of anticoagulants (i.e. warfarin or low molecular weight heparin), coagulants, anti-PLT (i.e. clopidogrel) 30 days prior to dosing;

11. Has scheduled any surgical procedure during study participation;
12. History of alcohol and/or drug abuse within 1 year prior to dosing, as judged by the PI and/or has a positive urine drug screen for substances of abuse including at a minimum marijuana, cocaine, methamphetamine, opiates, phencyclidine, barbiturates, benzodiazepines, tricyclic antidepressants, methadone, and amphetamines, at screening or check-in. Urine alcohol above 50mg/dL;
13. Has donated plasma or blood or intends to within 30 days prior to the first day of dosing and 30 days after the final day of dosing;
14. Has received treatment with any medication, either prescription or nonprescription, including dietary supplements or herbal medications (e.g., quercetin; Gingko Biloba; palmetto), within 14 days prior to dosing and is unable to refrain from any medication during the study period. Exceptions are acetaminophen (not more than 2g/day), vitamin products at recommended daily doses or hormonal birth control;
15. Has received any known hepatic or renal clearance altering agents (e.g., erythromycin, cimetidine, barbiturates, phenothiazines, or herbal/plant-derived preparations such as St. John's Wort) at any time during a period of 30 days prior to the administration of the study product;
16. Has a positive serology test for HIV antibodies, hepatitis B surface antigen, or hepatitis C virus antibody at screening;
17. Any subject with relevant food allergies (i.e. eggs or other components of standard clinic meals) or is unwilling to comply with diet restrictions;
18. Psychological and/or emotional problems, which would render the informed consent invalid, or limit the ability of the subject to comply with the study requirements;
19. Concurrent enrollment in any other clinical trial within 30 days; or
20. Subject is judged by the PI or Sponsor to be inappropriate for the study.

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

A randomization schedule will be prepared by the unblinded [redacted] statistician to randomly assign within each cohort six subjects to active treatment and two subjects to placebo. Enrollment is planned to occur at up to two sites. Envelopes containing the available randomization numbers and corresponding treatment assignments will be provided to the site(s) before the start of dosing. There may be two back-up subjects per cohort in the event of subject withdrawal prior to dosing.

Following review of all eligibility criteria, subjects will be assigned the next available randomization number by the unblinded site pharmacist and immediately dosed. Table 4 indicates the planned randomization numbers for this study. Details on the randomization procedures are provided in the Pharmacy Manual.

Table 4: Randomization Numbers

Cohort	Randomization Numbers
1	1001-1008
2	2001-2008
3	3001-3008
4	4001-4008
5	5001-5008

5.3.2 Masking Procedures

Masking will be carried out by use of a commercial, sugar-free taste-masking agent (commercially obtained OraSweet-SF). This ensures the active and placebo dose solutions match in appearance, taste, and consistency. The weight of UV-4B to be solubilized in the initial stock solution will be determined based on the number of subjects in that cohort and the planned dose as per Table 2**.** An additional intermediate dilution may be included if preferred by the site pharmacy for ease of making solutions. Appropriate volume of either WFI (placebo) or the solubilized drug substance solution will be transferred into an oral dosing container. Ten mL of the masking agent will be added, and the total volume made up to 30 mL with WFI.

5.3.3 Reasons for Withdrawal

Subjects will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. Data collected for withdrawn subjects will be evaluated for safety and PK.

Subjects may be withdrawn from the study for any of the following reasons:

1. Withdraws consent;
2. Noncompliance with study procedures and/or requirements;
3. Death;
4. Pregnancy;
5. In the opinion of the site PI and Sponsor, does not meet eligibility criteria upon admission to unit;
6. Has met Halting Criteria (see Section 9.7)
7. Administrative reasons/other.

In all cases of withdrawal, the reason for withdrawal will be recorded. Subjects who are withdrawn from the study will be asked to complete all Day 15 ± 1 safety assessments including follow-up of any AEs prior to termination from the study. Once randomized, subjects who withdraw from the study for any reason will not be replaced.

5.3.4 Blinding Procedures

Study subjects, the PI and study site personnel will remain blinded to all randomization assignments throughout the study. The Emergent medical monitor and personnel, [redacted] DMID medical monitor and NIAID personnel who are in regular contact with the study site and/or involved with documentation associated with the study will remain blinded to all subject randomization assignments. The PK analyst will be provided with dummy subject codes and remain blinded.

Selected individuals not involved in the conduct of the study (i.e. unblinded clinical monitor), including members of the SMC may have access to unblinded data as needed for safety review or other data review.

Pharmacist will remain unblinded during the course of the study.

5.3.5 Emergency Unblinding

Emergency unblinding of treatment assignment for a subject may be necessary due to a medical emergency, or any other significant medical event. Should an SAE or other circumstance require the blind to be broken to ensure a subject's safety, the PI should immediately notify Emergent (within 24 hours) to discuss the case and reason for unblinding (a written narrative must follow within 48 hours of the event).

Emergent Medical Monitor:

If emergency unblinding is required for a medical emergency:

1. The PI will make the decision to unblind the treatment assignment for AE's involving individual subjects;
2. An unblinding memo with the specific details for breaking the blind, including the rationale for unblinding and specific information regarding the subjects that are to be unblinded will be prepared by the site coordinator;
3. The document will be sent out for approval and signature to the PI, Emergent Medical Monitor and/or Sponsor Representative, as appropriate;
4. The original signed memo will be kept in the investigator site file and a copy of the signed document will be sent to the Sponsor;
5. The Site coordinator or designee will send the signed copy of the unblinding memo to the [redacted] unblinded pharmacist, who will send the randomization treatment to the PI (utilizing code break envelopes);
6. The PI will review the unblinding information, and, and continue to monitor/treat the subject as medically appropriate;
7. The [redacted] Clinical Project Manager will notify the study team that unblinding has occurred and will provide a copy of the unblinding memo as appropriate;
8. The Site Coordinator will notify the Institutional Review Board (IRB) that a request has been sent to the pharmacist to unblind the treatment assignment of a subject. Once available, the results of the unblind will be communicated to the IRB.

The treatment assignment is not to be provided to site personnel, including the PI at any time during the conduct of the study, except in the case of an emergency.

Procedures 2 through 8 listed above will be followed should a request come from the FDA to unblind a subject's treatment.

Any information regarding a subject being unblinded will be documented in the subject's study records. If the pharmacist is not on site, the code break envelopes will be available to the PI in case of emergency.

5.3.6 Termination of Study

Emergent, DMID, and the FDA may terminate the study in the interest of subject safety and welfare. In addition, DMID reserves the right to terminate the study at any time for any other

reason. If DMID terminates the study, the PI, IRB, SMC, Emergent, and the FDA will be informed, activities will be closed, and a study report will be prepared.

6 STUDY INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

Study product will be shipped to the clinic upon request by Emergent.

Sterile water for irrigation and OraSweet-SF will be obtained by the Pharmacy (section 6.1.2.2).

6.1.2 Formulation, Packaging, and Labeling

6.1.2.1 UV-4B

UV-4B for solubilization for the Phase 1b clinical program is manufactured, packaged, labeled, and released by [redacted]

Clinical trial material is UV-4B drug substance, packaged in double bags in containers in a configuration supported by previous and ongoing UV-4B stability programs. [redacted]

6.1.2.2 Sterile Water for Irrigation (WFI)

Sterile Water for Irrigation, USP is sterile, distilled, nonpyrogenic water for injection intended only for sterile irrigation, washing, rinsing, and dilution purposes. It contains no bacteriostat, antimicrobial agent or added buffer and is supplied only in single-dose containers. WFI will be used to solubilize the UV-4B drug substance, for intermediate UV-4B dilutions, and for placebo preparation.

6.1.2.3 OraSweet-SF

Commercially available OraSweet-SF contains purified water, glycerin, sorbitol, sodium saccharin, xanthum gum, and flavoring. It is buffered with citric acid and sodium citrate and contains methylparaben, potassium sorbate, and propylparaben as preservatives. OraSweet-SF will be used as a taste-masking agent. Use of OraSweet SF ensures the active and placebo dose solutions match in appearance, taste, and consistency. Masking procedures are described in Section 5.3.2.

6.1.3 Product Storage and Stability

6.1.3.1 UV-4B

For the study, containers of UV-4B will be shipped and stored under 2-8°C refrigerated conditions under locked and limited access.

[redacted]

6.1.3.2 Sterile Water for Irrigation (WFI)

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

6.1.3.3 OraSweet-SF

OraSweet-SF will be stored according to manufacturer specifications.

6.2 Dosage, Preparation, and Administration of Study Investigational Product

6.2.1 Dosage and Administration

UV-4B or Placebo will be administered orally as a 30mL oral solution TID for 7 days (every 8 hours ± 0.5 hours). A 50 mL rinse of the dosing container with tap water and an additional 160 mL of tap water will immediately follow each dose.

Details regarding planned dosing are included in Section 2.2 and in the Pharmacy Manual

6.2.2 UV-4B Preparation

At time of use, bulk drug substance will be removed from the container and weighed in the clinic pharmacy. An amount appropriate to the number of subjects being dosed and the dose to be administered will be solubilized in WFI. Gentle mixing by inversion will be used to solubilize the drug substance and generate a UV-4B stock solution. If required or convenient for the preparation of dilute dosing solutions, an intermediate dilution stock solution in WFI may be made. An appropriate volume of UV-4B stock solution will be removed using a syringe, and transferred into an oral dosing container. 10 mL of taste-masking agent (commercially obtained OraSweet-SF) will be added. If required, additional WFI will be added to increase the volume to 30 mL. The WFI and any glassware or plastic ware used for solubilization of the UV-4B and dilution and dosing of the drug substance will be sourced by the [redacted] Phase 1 unit. Detailed dose preparation instructions will be provided in the pharmacy manual.

6.2.3 Placebo Preparation

Placebo will be 10 mL of taste masking agent diluted to 30 mL with WFI. Detailed dose preparation instructions will be provided in the pharmacy manual.

Consumption of water will be restricted, other than what is required for study product dilution and rinsing, for one hour prior to dosing and for 1 hour post dosing.

The dates and times of UV-4B administration will be recorded in the subjects' electronic Case Report Form (eCRF).

6.3 Accountability Procedures for the Study Investigational Product

The Research Pharmacist (or designee) will keep a record of the dates and amounts of study product received (including packing slips), the amount dispensed to study subjects, any amount destroyed, and the amount unused. Product accountability will be recorded by the Research Pharmacist on a Product Disposition Record or equivalent document with a separate accountability record for study product and placebo. Upon completion of product accountability, all unused study product will be returned or destroyed per Emergent requirements and instructions once the relevant accountability records and monitoring visit report have been submitted to Emergent.

6.4 Assessment of Subject Compliance with Study Investigational Product

Study product is administered to the study subjects during the in-clinic phase by appropriately trained and designated clinic personnel. Dose administration information such as date/time, complete, or incomplete dosing will be documented in the source documentation and in the eCRF for each subject by the study personnel (see Section 7.3.1).

All subjects will be administered the assigned study product or placebo TID (every 8 hours ± 0.5) for 7 days. The total volume of each dose of the study product solution plus the rinse(s) and water will be 240 mL.

The following procedures will be instituted in cases of incomplete or interrupted dosing of subjects:

- In the event of partial dosing, either due to dosing error, or the subject coughing, gagging or spilling solution, the subject will only be followed for safety measurements as defined in Section 5.3.3. PK samples will not be taken.

6.5 Concomitant Medications/Treatments

All medications taken by a subject for the 30 days prior to enrollment will be documented in the study record. All concomitant medications that are administered during the study must be used for the treatment of an AE (other than oral contraceptives) and must be recorded in the eCRF for each subject and in the subject's source documents. All medications (other than acetaminophen) must be authorized by the clinic PI (or designee).

7 STUDY SCHEDULE

7.1 Day -21 to Day -2 (Screening)

After providing written informed consent, each subject will be assigned a screening number and undergo an eligibility screening. The following will be obtained during the screening period (within 21 days prior to administration of the study product):

- Review inclusion and exclusion criteria;
- Obtain medical history including current medical diagnoses, major surgical procedures, and medication history including prescription and nonprescription medication (i.e. dietary supplements or herbal medications taken within 30 days prior to Day 1);
- Obtain history of alcohol use, abuse, or dependence;
- Record demographics including date of birth, gender, ethnicity and race;
- Complete a physical examination including vital signs (SBP and DBP, pulse rate, respiration rate, and oral temperature after being supine for 10 minutes), orthostatic blood pressure and pulse rate (taken after 2 minutes in standing position), height, weight, and calculation of BMI. If abnormal, these measurements may be repeated once;
- Obtain blood samples for clinical chemistry, hematology, coagulation tests, urinalysis, serum and urine pregnancy tests (if female), FSH (if post-menopausal), HIV, hepatitis B surface antigen, and hepatitis C antibody;
- Obtain urine sample for drugs of abuse and cotinine; (see Section 8.2.1);
- Obtain urine test for alcohol;
- Obtain 12-lead ECG;
- Distribute a fecal occult blood card with instructions for use and return of card to the clinic on or before Day - 1;
- Review concomitant medication usage.

7.2 Enrollment/Baseline

7.2.1 Day -1 (Admission to Clinic; approximately 24 hours prior to dosing)

Eligible subjects will return to the clinic on Day -1 for the procedures listed below.

- Review inclusion/exclusion criteria. If screening criteria are satisfied, the subject may be admitted to the clinic.
- Confirm that subject adhered to dietary restrictions for previous 72 hours;
- Complete an abbreviated physical examination (general appearance, heart, lungs, skin, and abdomen), skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and evidence of hematoma, ecchymosis or petechia) and brief neurological examination (mental status, motor system, and sensory system);
- Obtain vital signs (blood pressure, pulse rate, after being supine for 10 minutes, and orthostatic blood pressure and pulse rate (taken after 2 minutes in the standing position), respiratory rate and oral temperature;
- Obtain weight;
- Obtain urine sample for drugs of abuse and cotinine;
- Obtain urine test for alcohol;
- Obtain serum and urine pregnancy tests (if female);
- Obtain baseline clinical chemistry, hematology, coagulation, and urinalysis. Must have no values that are Grade 2 or higher based on the toxicity grading scale in Appendix II;
- Obtain fecal occult blood assessment from kits sent home at screening (if not already assessed). Must have at least 1 negative and no positive values;
- Obtain 2nd 12-lead ECG (Day -1) on the morning of admission. All remaining in-clinic ECGs are obtained at the same time each day during treatment period (within a 2 hour window of the previous ECG);
- Telemetry for at least 4 hours while awake;
- Sham dose consisting of masking solution, 240 mL (total volume) of diluent will be administered on Day -1; subjects must be able to comply with dose solution (30 mL), the 50 mL rinse of dosing container with tap water immediately after dose and the 160 mL of tap water for enrollment into the study;
- Review concomitant medication usage;

7.3 Treatment Period

The specific order of evaluations conducted during the treatment period will be defined by the [redacted] Biometrics system.

7.3.1 Day 1

Prior to the administration of the first dose of study product, the following procedures will be performed:

- Brief physical examination focused on the examination of skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and evidence of hematoma, ecchymosis or petechia), brief neurological examination (mental status, motor system, and sensory system);
- Confirm that subject adhered to fasting requirements of at least 3 hours before the first dosing;
- Obtain vital signs (blood pressure, pulse rate, after being supine for 10 minutes, and orthostatic blood pressure and pulse rate (taken after 2 minutes in the standing position), respiratory rate and oral temperature;
- Obtain a triplicate 12-lead ECG;
- Obtain baseline blood sample for PK analysis (t=0), to be taken within 1 hour prior to first dose;
- Telemetry starting at -0.5 hours on Day 1 through at least 4 hours post the first dose;
- Randomization

All subjects will be administered the assigned study product or placebo. The total volume of each dose of the study product solution plus the rinse(s) and water will be 240 mL.

- The following procedures will be instituted to reduce incomplete or interrupted dosing of subjects:
  In the event of partial dosing, either due to dosing error, or the subject coughing, gagging or spilling solution, the subject will only be followed for safety measurements as defined in Section 5.3.3.

Following the administration of study product, the following procedures will be performed:
All physical exams, blood tests and ECGs after subjects have been dosed are obtained at approximately the same time each morning (within 2 hours).

- Obtain clinical chemistry, hematology, and coagulation;
- Obtain blood samples for PK analysis at 0.25 (±5 min), 0.5 (±5 min), 1 (±10 min), 1.5 (±10 min), 2 (±10 min), 2.5 (±15 min), 3 (±15 min), 5 (±30 min), 6 (±30 min), 8 (±30 min) hours (8 hour sample to be collected immediately before the second dose).
- Obtain vital signs (blood pressure and pulse rate including oral temperature and respiratory rate) at 1, 2, 3, 4, 5, 6 and 7 hours (±15 minutes), after each administration of the study product. Vital signs should be taken after being supine for 10 minutes,

and orthostatic blood pressure and pulse rate (taken after 2 minutes in the standing position);

- Telemetry through at least 4 hours post first dose;
- Obtain fecal occult blood assessment starting approximately 6 hours post first dose on every stool sample. Stool volume and frequency will be recorded;
- Obtain occult blood on all vomitus;
- Perform brief physical examination focused on the examination of skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and cutaneous) 30 (+ 15) minutes after the first dose;
- Review concomitant medication usage once daily;
- Completed AE assessment (including SAEs) will be recorded on AE source forms throughout the study and placed in the subject's clinic records.

Subjects will receive standardized meals as follows on Day 1: lunch 4 hours post first dose and dinner after completion of procedures scheduled at those times; subjects will also receive a light evening snack. A drink will also be provided with each of the meals. No breakfast will be served on Day 1. Dosing will occur TID every 8 hours ± 0.5hour.

7.3.2 Day 2 through Day 7 (In-Clinic)

All subjects will be administered the assigned study product or placebo according to the dosing schedule. If a subject has a missed or incomplete dose as described above (Section 7.3.1) the subject will continue to the next dose as planned. Subjects will not be allowed to miss more than four (4) doses after achieving predicted steady state (i.e. after the third dose on day 1) while participating in the study. If a subject misses four (4) or less doses their continued participation in the study will be determined by the PI and the Emergent and NIAID medical monitors on a case by case basis.

As per Section 7.3.1, all physical exams, blood tests and ECGs after subjects have been dosed are obtained at approximately the same time each morning after dosing (within 2 hours).

- Brief physical examination focused on the examination of skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and cutaneous); symptom directed/targeted examination based on subject symptoms and brief neurological examination (mental status, motor system, and sensory system);
- Obtain vital signs (blood pressure, pulse rate), after being supine for 10 minutes, and orthostatic blood pressure and pulse rate (taken after 2 minutes in the standing position), respiratory rate and oral temperature;
- Obtain clinical chemistry, hematology, coagulation, and urinalysis;

- Obtain fecal occult blood assessment on every stool sample or less frequent as per discretion of the PI. Stool volume and frequency will be recorded;
- Obtain occult blood on all vomitus
- Obtain 12-lead ECG at same time each day (within 2 hours);telemetry starting 0.5 hours prior to the third (3rd) dose on Day 7 continuously through 4 hours post dose;
- Obtain blood samples for PK analysis Days 2-6: one trough sample daily within fifteen (15) minutes before the first dose approximately the same time each day (±10 min);
- Obtain blood samples on Day 7: immediately (within fifteen minutes) before the final dose, and at 0.25 (±5 min), 0.5 (±5 min), 1 (±10 min), 1.5 (±10 min), 2 (±10 min), 2.5 (±15 min), 3 (±15 min), 5 (±30 min), 6 (±30 min), 8 (±30 min), 10 (±30 min), 12 (±30 min), and 14 (±30 min) hours after the final dose;
- Review concomitant medication usage;
- Complete AE assessment (including SAEs) which will be recorded on AE source forms throughout the study and placed in the subject's clinic records. Data from the AE source form will be entered in the Electronic data capture (EDC) system. All AEs will be monitored until they are resolved or determined by the site PI to be medically stable.

7.3.3 Day 8 (Discharge from Clinic)

The following procedures will be performed:

- Abbreviated physical examination (general appearance, heart, lungs, skin, and abdomen), and brief neurological examination (mental status, motor system, and sensory system). Also perform brief physical examination focused on the examination of skin and oropharyngeal mucosa for evidence of for bleeding and/or bruising (oral [gums] and cutaneous);
- Obtain vital signs (blood pressure, pulse rate), after being supine for 10 minutes, and orthostatic blood pressure and pulse rate (taken after 2 minutes in the standing position), respiratory rate and oral temperature; and weight;
- Obtain clinical chemistry, hematology, coagulation, and urinalysis;
- Obtain fecal occult blood assessment prior to discharge if stool available prior to discharge. Subjects may receive a fecal occult blood card per discretion of the PI with instructions for use and return of card to the clinic at a subsequent visit. Stool volume and frequency will be recorded;
- Obtain occult blood on all vomitus

- Obtain 12-lead ECG;
- Obtain blood sample for PK analysis as described in the schedule of events table (Appendix IV);
- Review concomitant medication usage;
- Complete AE assessment (including SAEs) which will be recorded on AE source forms throughout the study and placed in the subjects' clinic records. Data from the AE source form will be entered in the EDC system. All AEs will be monitored until they are resolved or determined by the site PI to be medically stable;
- Discharge from the clinic, with instructions to return on Day 10 ± 1.

7.3.4 Day 10 ± 1 (Outpatient Visit)

The following procedures will be performed:

- Abbreviated physical examination (general appearance, heart, lungs, skin, and abdomen) and brief neurological examination (mental status, motor system, and sensory system). Also perform brief physical examination focused on the examination of skin and oropharyngeal mucosa for evidence of for bleeding and/or bruising (oral [gums] and cutaneous);
- Obtain vital signs (blood pressure, pulse rate, after being supine for 10 minutes, respiratory rate and oral temperature);
- Obtain clinical chemistry, hematology, coagulation, and urinalysis;
- Obtain 12-lead ECG;
- Obtain blood sample for PK analysis. Note: this is an optional sample, if warranted by the PK results from earlier cohort or cohorts;
- Review concomitant medication usage;
- Complete AE assessment (including SAEs) which will be recorded on AE source forms throughout the study and placed in the subject's clinic records. Data from the AE source form will be entered in the EDC system. All AEs will be monitored until they are resolved or determined by the site PI to be medically stable;
- Provide instructions to return on Day 15±1.

7.4 Day 15 ±1 (Final Study Visit)

The following procedures will be performed:

- Complete a physical examination including vital signs (blood pressure, pulse rate, respiration rate, and oral temperature after being supine for 10 minutes), and body weight;
- Obtain serum pregnancy test (females only);
- Obtain clinical chemistry, hematology, coagulation, and urinalysis;
- Obtain vital signs (blood pressure, pulse rate, after being supine for 10 minutes, respiratory rate and oral temperature);
- Obtain 12-lead ECG;
- Fecal occult blood assessment at follow-up will be performed as per discretion of the PI, if positive will continue to follow until resolution;
- Review concomitant medication usage;
- Complete AE assessment (including SAEs) which will be recorded on AE source forms throughout the study and placed in the subject's clinic records. Data from the AE source form will be entered in the EDC system. All AEs will be monitored until they are resolved or determined by the site PI to be medically stable.

A tabulated schedule of events is provided in Appendix IV.

7.5 Early Termination Visit

The clinic will make every effort to perform all assessments outlined for the follow-up visit (Day 15±1) if a subject is terminated prematurely from the study. All information collected will be documented in the subjects study records including eCRF.

7.6 Unscheduled Visits

Data from unscheduled visits or procedures (if any) will be captured in the EDC system and presented in data listings. These data will be clearly identified as unscheduled observations. Safety assessments including updated history and the following onsite evaluations: AE, PE, and any other study procedures deemed necessary by the PI will be obtained.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

During screening, a medical history, including a current medication history, will be obtained by interview and, if available, medical records. Additionally, demographic data, including gender, date of birth, race, and ethnic origin, and a history of alcohol abuse or dependence will be collected at screening.

A complete physical examination, including vital signs, examination of the skin; head, eyes, ears, nose, and throat; lymph nodes; heart; lungs; abdomen; extremities; and joints will be performed at screening and the final follow-up visit. This examination will also include an assessment for stigmata of hepatorenal insufficiency, anemia, coagulopathy, addiction, etc. Breast and genital examinations will not be performed. The complete physical examination will include weight (without shoes and wearing lightest possible clothing). The complete physical examination at screening will also include height and calculation of the BMI and 12-lead ECG. An abbreviated physical examination (general appearance, heart, lungs, skin, and abdomen) and brief neurological examination (mental status, motor system, and sensory system) will be done daily. Additionally, brief examinations focused on skin and mouth for bleeding and/or bruising (oral [gums] and cutaneous) will be performed daily. A targeted physical examination (i.e. hematologic/bleeding and neurological) will be conducted in response to any AE, as determined by the site PI and the grading of the AE will then be determined.

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

Laboratory assessments will be done at screening, check-in (Day -1), Days 1 through 8, 10 (±1) and 15 (±1) unless otherwise noted at approximately the same time each day (within 10 minutes). The following specific tests will be performed as per Appendix IV.

Screening:

- Serology will include hepatitis B surface antigen, antibodies to hepatitis C, and antibodies to HIV.
- Urine: Toxicology screen to include at a minimum marijuana, cocaine, methamphetamine, opiates, phencyclidine, barbiturates, benzodiazepines, tricyclic antidepressants, methadone, and amphetamines. Cotinine level, pregnancy; urine alcohol levels; and urinalysis with microscopic examination;

- Serum: Comprehensive metabolic profile (chemistry 17), complete hepatic panel to include LDH, γ-glutamyltransferase (GGT), AST, ALT and direct and indirect bilirubin. Serum fertility panel to include human chorionic gonadotropin (HCG) to exclude pregnancy and FSH to confirm menopausal/amenorrheic status;
- Hematologic/coagulation: Complete blood count with differential and quantitative PLTs. Coagulation studies will include international normalized ratio (INR), PT, and aPTT. Samples for select hematology (PLT count);
- Fecal Occult Blood Assessment: At screening, subjects will be given a fecal occult blood card with instructions for use and return of the card to the clinic on or before Day -1. This sample will serve as the pre-dose assessment.

Check-in Day -1:

- Urine: Toxicology screen to include at a minimum marijuana, cocaine, methamphetamine, opiates, phencyclidine, barbiturates, benzodiazepines, tricyclic antidepressants, methadone, and amphetamines. Cotinine level, pregnancy; urine alcohol levels; and urinalysis with microscopic examination;
- Serum: Comprehensive metabolic profile (chemistry 17), complete hepatic panel to include LDH, GGT, AST, ALT and direct and indirect bilirubin, and pregnancy;
- Hematologic/coagulation: Complete blood count with differential and quantitative PLTs. Coagulation studies will include INR, PT, and aPTT;
- Fecal Occult Blood Assessment: If not already done, the returned screening test card will be assessed for evidence of fecal occult blood.

The Day -1 laboratory test results (serum chemistry/hematology/urinalysis) are considered as baseline. Laboratory reports will be available before dosing on Day 1 and must be promptly reviewed by the PI. Any subjects having one or more baseline laboratory test results meeting Grade 2 or higher criteria on the toxicity grading scale in Appendix II are ineligible for study participation.

Days 1 through 8 and follow ups on Day 10 (±1) and Day 15 (±1):

- Hematology, clinical chemistry, & coagulation: A subset of hematology (PLT count), serum chemistry (AST, ALT), and coagulation (INR, PT, aPTT) assessments will be collected prior to the first dose only on Day 1. Full clinical chemistry, hematology, coagulation, and urinalysis testing will be performed on Days 2 through 8 and follow ups on Day 10 (±1) and Day 15 (±1).

- Fecal Occult Blood Assessment: Fecal occult blood assessments will be performed on Days 1 through 8 and Day 15. If any fecal occult blood test is positive during the study period, subject(s) will be evaluated and a test will be performed on all subsequent stool specimens until negative. If fecal occult blood remains positive (excluding for hemorrhoids) for 3 consecutive samples, subjects will be referred for a GI evaluation and will be withdrawn from the study.

- Vomitus Occult Blood: Occult blood assessments will be done on all vomitus.

All laboratory assessments will be done by the clinical site's certified laboratory. Laboratory toxicity grading will be determined by use of the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* and the *Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007,* as modified for this study and appropriate for the administration of UV-4B (Appendix II).

Table 5: Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Occult Blood
RBC count	Alkaline phosphatase	INR[b]	pH	Fecal
RBC distribution width	ALT[b]	PT[b]	Specific gravity	Vomitus
WBC count[c]	AST[b]	aPTT[b]	Glucose	
Basophils	Total bilirubin		Ketones	
Eosinophils	Indirect Bilirubin			
Lymphocytes	Gamma-glutamyltransferase		Leukocyte esterase	
Monocytes	Lactate dehydrogenase[a]		Nitrites	
Neutrophils	Blood urea nitrogen		Occult blood	
Hematocrit	Creatinine		Protein	
Hemoglobin	Uric acid		RBCs/hpf	
Mean corpuscular hemoglobin	Sodium		WBCs/hpf	
Mean corpuscular hemoglobin concentration	Chloride		Bacteria	
Reticulocyte count	Carbon dioxide		Casts	
MCV	Potassium		Epithelial cells	
Platelet count[b]	Creatine phosphokinase[a]		Mucous threads	
	Albumin		Crystals	
	Calcium			
	Magnesium			
	Protein (total)			
	Amylase			
	Lipase			

[a] If either lactate dehydrogenase or creatine phosphokinase is elevated (i.e., Grade 2 or higher, or otherwise deemed clinically significant by the PI), iso-enzyme levels will be determined using investigative assays.
[b] Samples for select hematology (PLT count), serum chemistry (AST and ALT), and coagulation (INR, PT, aPTT) assessments will be collected on Day 1 prior to the first dose of study product.
[c] Differential should include absolute values.

8.2.2 Special Assays or Procedures

Blood samples for UV-4 PK analysis will be collected in tubes containing K2EDTA as the anticoagulant on the days specified in Section 7 and Appendix IV. The actual date and time of collection of each sample will be recorded on the appropriate section of the eCRF.

The total volume of blood that will be drawn from each subject in this study is described in Table 6.

Table 6: Volume of blood to be drawn from each Subject

Type	Laboratory Test	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Safety	Clinical chemistry	8.5	11	93.5
	ALT and AST only	3.5	1	3.5
	Hematology	2	11	22
	Coagulation	20.7	11	227.7
	aPTT, PT, INR	2.7	1	2.7
	Platelet count	2.7	1	2.7
	Serology	8.5	1	8.5
	future assays[a]	2	1	2
Pharmacokinetic		3	31	93
When using an indwelling catheter 1.0 mL of blood will be removed prior to sample collection		1	31	31
Total		**54.6**	**100**	**486.6**

[a] Blood samples will be stored to allow for the option to test for additional parameters including cytokine analysis.

8.2.3 Specimen Preparation, Handling, and Shipping

8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

The collected PK blood samples (3 mL) will be placed on ice after blood draw, and within 1 hour centrifuged at room temperature at approximately 3000 revolutions per minute for 15 minutes. Plasma will then be harvested and split into 3 aliquots of approximately 250 µL (any additional plasma placed in a fourth tube as a back-up sample) and stored frozen at -20°C until shipped.

Analysis of plasma for UV-4 will be performed by the qualified bioanalytical laboratory, [redacted] Instructions for the proper preparation, handling, storage and shipping of specimens will be provided separately in a study-specific laboratory manual (i.e., Bio-packet).

8.2.3.2 Specimen Shipment

Details regarding shipment of plasma samples can be found in the laboratory manual.

8.3 Diet, Exercise, and Study Restrictions

Enrolled subjects will be advised to abstain from strenuous exercise starting 96 hours (4 days) prior to dosing on Day 1 and continuing through the in-subject stay and for at least 96 hours prior to the follow-up visits. In addition, enrolled subjects will be advised to stop consumption of caffeine-containing beverages (e.g., coffee, tea, cola, energy drinks, and cacao [chocolate]) for 72 hours before first dose and refrain from using them during the in-subject stay(s) of the study. Alcohol consumption will not be allowed during the entire study (from 72 hours before dosing through follow-up). Additional food and drinks that are not permitted 72 hours prior to and during the in-subject treatment period of the study are grapefruit or grapefruit juice, Seville oranges or orange marmalade.

Subjects will be instructed to maintain a diet that will assist in preventing a false positive reading for fecal occult blood. Such a diet excludes: red meat (no beef, lamb, or liver in any form) and vegetables high in peroxidase (turnips, radishes, and horseradish). Vitamin C is limited to ≤ 250 mg/day. Subjects will be given a diet guideline at screening. Subjects will be advised that if accepted for the study they should follow the dietary guidelines for fecal occult blood 72 hours prior to check-in.

Enrolled subjects will remain in the study unit from the time of admission on Day -1 until discharge from the unit on Day 8. During that period of time they will consume a normal house diet (defined as a standard diet that doesn't allow for substitutions and is received by all subjects) served at standard times (breakfast, lunch, and dinner) and will have access to snacks as permitted.

Prior to dosing on Day 1, subjects will not eat any food at least 3 hours before the first dose. Consumption of water and food will not be restricted except for 1 hour before to 1 hour after dosing for all subsequent doses (except for approximately 240 mL (total volume) allocated for study product solution plus rinse and water). Lunch, dinner, and an evening snack will be provided.

During the follow-up period it is recommended that subjects continue eating a balanced diet, and avoid consumption of caffeine-containing beverages.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Safety is the primary objective.

9.1.1 Adverse Events

Adverse events will be evaluated from time of the first dose administration through the last follow-up visit. AEs that have not resolved at the Day 15 (± 1) follow-up visit will be followed until resolution or until medically stable.

9.1.2 Vital Signs

Vital signs (after being supine for 10 minutes) including SBP and DBP (mmHg), pulse rate (beats/minute), respiratory rate (breaths/minute), and oral temperature (°C) will be obtained and recorded according to the time points in the schedule of events (Appendix IV). Systolic and diastolic blood pressure and pulse rate will also be obtained after 2 minutes standing and recorded according to the time points in the schedule of events. If a vital sign measurement is observed to be abnormal, it may be repeated up to a total of 2 times at 5 to 10 minutes intervals. If a normal value is obtained, no further repeat measurements are required. If the value is still abnormal after 2 repeats, the least abnormal value will be utilized for grading the AE. The AE will be considered ongoing until a future measurement shows resolution. The subject may be referred to a primary care provider if the abnormality does not resolve and, according to the study clinicians, requires medical care. Vital sign values of Grade 1 or higher according to toxicity grading criteria listed in Appendix II will be reported as AEs.

9.1.3 Electrocardiograms

A 12-lead ECG will be performed at approximately the same time each day. Subjects will be placed in a supine position for at least 10 minutes prior to recording an ECG. Triplicate 12-lead ECGs will be collected at the pre-dose on Day 1 (baseline) and a single ECG will be collected at other scheduled times. The screening and Day 1 ECG will be used by the PI to determine subject's eligibility for enrollment. The Day 1 ECG will be reviewed to determine if subjects are safe and appropriate to dose and will be used to determine baseline for waveform and QTc.

All ECGs will be reviewed by the PI or designee. ECGs with the following readings will be considered acceptable for study and will not be considered abnormal for study purposes unless the PI or physician designee believes they represent a new medical condition when compared to baseline ECGs. In such cases an AE will be documented and the subject will be

followed for safety evaluations as appropriate. The following pre-existing conditions identified at enrollment will not be considered adverse events:

- sinus bradycardia;
- sinus arrhythmia;
- early repolarization;
- nonspecific ST-T wave pattern or changes, mild or moderate right axis deviation;
- first degree AV block (PR interval less than 210ms is acceptable);
- nonspecific intraventricular conduction delay (QRS, or average of triplicate QRS; less than 120ms is acceptable);
- short PR interval (where no delta wave), and indeterminate axis.

The Sponsor may review all or individual screening or Day -1 ECGs or may delegate to determine if meets intention of entry criteria goal of enrolling healthy normal study subjects.

Three ECG tracings are made pre-dose. At least 2 of the 3 tracings should be acceptable/normal per (correct) machine reading and all three must be consistent with otherwise healthy normal individuals.

If a post-dose ECG demonstrates a prolonged QTc interval (>500ms) or an increase of at least 60ms from baseline average, 2 more tracings should be captured within 10 minutes. The averaged QTc value of these 3 will be used for decision making relative to the halting rules described in Section 9.6.

In the event of a prolongation of QTc post dosing, the site will start telemetry monitoring of the subject and capture triplicate 12 lead ECG (3 tracings within a 5 minute period) every 30 minutes until the average for the triplicates has returned within 60ms of the baseline value at which time telemetry maybe discontinued. Persistent (1 hour or more) elevation in QTc (>500ms) should prompt immediate consideration of transfer to appropriate emergency department for further evaluation, monitoring, and/or treatment.

In the event of a change in ECG wave forms consistent with a change in cardiac function or conduction when compared to baseline tracings, or in the event of a subject with possible cardiac related symptoms, repeat ECG should be obtained every 30 minutes until wave form change reverts to baseline appearance, or symptoms resolve, or are determined not to be cardiac in origin. Subjects with cardiac related symptoms associated with ECG changes will be transferred to appropriate emergency department for further evaluation and treatment.

9.1.4 Telemetry

A 5-lead real-time telemetry ECG will be displayed for at least 4 hours on Day -1 while awake and again starting at -0.5 hours on Day 1 through at least 4 hours post initial-dose;

starting at 0.5 hours prior to the 3rd dose on Day 7 continuously through 4 hours post dose. (PI discretion based on ECG results) Any clinically relevant changes from baseline (Day 1, 4-hour recording) will be documented by a 12-lead ECG or an appropriate rhythm strip. These findings will be recorded in the subject's eCRF. Telemetry will be monitored by the PI, research nurse, or designee.

9.1.5 Physical Examination

A complete physical examination, including examination of the skin, head, eyes, ears, nose, and throat; lymph nodes, heart; lungs; abdomen; extremities; and joints will be performed at screening and Day 15 (±1) the follow-up visit. Breast, genital, and rectal examinations will not be performed. The complete physical examination at screening will also include height, weight and calculation of the BMI.

An abbreviated physical examination (general appearance, heart, lungs, skin, and abdomen) and abbreviated neurological examination (mental status, motor system, and sensory system) will be done (Day -1 through 8), and on Day 10 (±1).

Brief physical examinations focused on examination of skin and oropharyngeal mucosa for evidence of for bleeding and/or bruising (oral [gums] and cutaneous) will be performed on each day while admitted to the clinic (Day -1 through 8) and on Day 10 (±1).

Targeted physical examinations will be done at other study time points if an AE is reported or if the PI or designee feels that it is in the best interest of the study subject.

9.1.6 Clinical Laboratory Testing

Laboratory testing will be utilized to evaluate safety on an ongoing basis through the treatment and follow-up periods according to Section 8.2. Laboratory reports from the local clinical laboratory will be provided to the clinic on the same day as sample collection and will be filed in the subjects' charts. Any values outside of the laboratory defined range will be flagged as such by the clinical laboratory.

9.1.7 Evaluation of Hypersensitivity Reactions

Examples of hypersensitivity (HS) reactions include erythema of oropharyngeal and conjuctival membranes, rhinitis, coryza, breathing difficulties including wheezing, dyspnea and stridor, and dermatologic findings to include diffuse pruritus, macular rashes and or vesiculation. Laboratory abnormalities suggestive of HS reaction (e.g., peripheral eosinophilia) require clinical corroboration.

Any evidence of HS reaction during study requires cessation of dosing pending physician evaluation and clinical corroboration. If HS reaction follows dosing, AE or SAE will be

recorded in accordance with physical monitoring criteria or laboratory abnormalities noted in Appendix II.

The Phase 1 treatment facility is capable of managing all types of HS reactions from HS type I-IV (e.g., with bedside epinephrine, diphenhydramine, terbutaline and albuterol nebulizers and oral and/or systemic steroids). [redacted] will follow their Standard Operating Procedures (SOPs) for treatment of HS reactions. Please see general anaphylaxis protocol (Appendix V).

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for "SAEs" should be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include Medical Doctor, Physician's Assistant, Nurse Practitioner, Doctor of Osteopathy, or Dentist), and time of resolution/stabilization of the event. All AEs occurring while in study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution as determined by the PI.

Any medical or laboratory condition that is present at the time that the subject is screened up through ingestion of the first dose should be considered as baseline/pre-existing condition and not reported as an AE. However, if it deteriorates at any time during the study after ingestion of the first dose, it should be recorded as an AE.

All AEs must be assessed for severity and relationship to study product. The PI will make an assessment of severity for each AE and SAE reported during the study and will assign it to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities;

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities;

Severe: An event that prevents normal everyday activities

In addition, all AEs will be graded (Grade 1 to 4) according to the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* and the *Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007* as modified for this study (Appendix II). For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0=absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.

Relationship to Study Products: The PI's assessment of an AE's relationship to the study product is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. All AEs must have their relationship to study product assessed using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines will be used.

Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE. If an alternate etiology is not identified, the AE must be considered related to study product.

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

AE's should be documented from time of dose administration through the final study visit.

9.2.2 Serious Adverse Events

Serious Adverse Event: An AE or suspected adverse reaction is considered "serious" if, in the view of either the PI or Sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening: an AE is considered "life-threatening" if, in the view of either the PI or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE, had it occurred in a more severe form, might have caused death;
- Requires hospitalization or prolongation of existing hospitalization;
- Results in disability/incapacity;
- Is a congenital anomaly or birth defect; or
- Is considered an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include

allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

All SAEs will be:

- Recorded on the appropriate eCRF;
- Followed through to resolution by a study PI;
- Reviewed and evaluated by a study PI.
- Recorded on the SAE Data Form and forwarded within 24 hours by fax or email to Emergent Pharmacovigilance.
- Sent to DMID Medical Monitor

Dosing will be paused for any SAE until causality is fully assessed by the PI and SMC. Dosing will cease if the SAE is determined to be either drug-related or unknown, and may resume if the SAE is determined to be not drug-related by the PI and SMC.

SAE's should be documented from time of dose administration through the final study visit.

9.2.3 Procedures to be followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

The collection of laboratory data is listed in Section 8.2.1. The normal reference ranges utilized in this study are shown in the current version of the Laboratory Protocol Reference Ranges published by Lab. The grading of abnormal clinical findings are based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* and *Division Of Microbiology And Infectious Diseases (DMID) Adult Toxicity Table November 2007* as modified for this study (see Appendix II).

Any medical condition or graded laboratory value (according to Appendix II) after ingestion of the first dose or deterioration from the baseline condition will be reported and followed as an AE or, as appropriate, SAE. Attempts will be made to follow the subject closely to determine the outcome and duration of an event. Additional assessments including the repeat of laboratory tests and ECGs will be performed in an effort to monitor the subject as appropriate. If an event is ongoing at the time of study termination, permission will be requested from the subject to continue follow-up until the site PI or designee deems the event to be resolved, chronic, or the subject's condition to be medically stable. Abnormal ECGs, at the discretion of the PI, will be reviewed by a cardiologist.

9.3 Reporting Procedures

Adverse events will be reported using the designated AE form. All SAEs , medication toxicities, deaths, or hospitalizations (other than elective) occurring following administration of study product will be recorded using the SAE Form and reported to the IRB and Emergent Medical Monitor, CROMS, NIAID's designated pharmacovigilance contractor and the Independent Safety Monitor (ISM), by fax in the mandatory time frame described below, including those events deemed unrelated to the protocol. Each event will be described in detail along with start and stop dates, relationship to investigational product, action taken, and outcome. Adverse events will be assessed in terms of their seriousness, intensity, and relationship to study product. Events that resulted in planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study or before study product was given, are not to be considered AEs unless they cause the planned hospital admission or surgical procedure to occur at a time other than the planned date.

9.3.1 Serious Adverse Events

Any SAE, including death due to any cause, that occurs to any subject entered into treatment in this study whether or not considered related to the study product, must be reported to the Sponsor or their representative by telephone and in writing within 24 hours of the PI knowing of the event.

Following notification from the PI, Emergent will report any suspected adverse reaction that is both serious and unexpected. Emergent will notify FDA, all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) and DMID in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Emergent will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Emergent will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

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

9.3.2 Reporting of Pregnancy

A Notification of Pregnancy form will be completed for any female study subject or for any female partner of a male study subject who becomes pregnant following their exposure to

study product (Day 1) through 3 months after the last dose of study product and forwarded within 24 hours of awareness by fax or e-mail to Emergent Pharmacovigilance. All pregnancies will also be reported as a protocol deviation. The site will maintain contact through at least monthly telephone calls with pregnant study subjects to obtain pregnancy outcome information. The pregnant subject will be followed by monthly telephone calls until 2 months after the birth of the baby or until the end of the pregnancy (in case pregnancy is terminated) at which time the Pregnancy Outcome form will be completed and forwarded to Emergent Pharmacovigilance. Infants born to these study subjects will also be monitored for SAEs for up to 2 months after birth (information regarding SAEs will be captured on the Pregnancy Outcome form and the SAE form). Pregnancy Outcome forms will be limited to collecting data on the following information, should it be identified during the monthly telephone calls, at the end of the pregnancy, or at the follow-up telephone call at 2 months after birth of the baby:

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

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

The collection of laboratory data will be limited to those parameters listed in Section 8.2.1. Abnormal laboratory test values or abnormal clinical findings such as heart rate will be recorded using the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* (with the exception of sodium and potassium [see Section 9.2.1]). However, the grading is modified for sodium and potassium since there is significant overlap between laboratory normal values and Grade 1 and 2 toxicity criteria using this grading scale (Section 9.2.1). The QT interval will be corrected using the Fridericia formula (QTcF). All AEs will be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

9.5 Dose Escalation

The SMC will review all safety and PK data after completion of each cohort. Upon completion of review by the SMC, safety summary and PK data will be sent to the FDA for review and approval to continue with dose escalation.

9.6 Study Halting Criteria

General:

- Any SAE
- Three or more subjects within a cohort, with the same Grade 2 event ;
- Any single Grade 3 or above finding (with the exception of aPTT as explained below);
- Evidence of hematemesis or hematochezia in 2 or more subjects
- Any other findings that, at the discretion of the PI, indicate that the study should be halted;

Electrocardiograph (ECG):

Two or more subjects within a cohort who meet any of the criteria below:

- PR: >220 ms
- QRS: >120 ms
- QTcF > 450 ms for men and >470 ms for women; or
- Change from baseline (average of pre-dose triplicate ECGs): QTcF >60 ms.

Decisions are to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, 2 more ECGs should be obtained over a 10 minute period. The averaged QTcF values of the 3 ECGs will then be used for decision making.

Laboratory criteria:

- Two or more subjects within a cohort have a Grade 3 increase in aPTT (confirmed on repeat) as defined by the FDA toxicity grading scale as modified for this study and as appropriate for the administration of UV-4B (Appendix II).

If any of the above events occur, the study will be halted and the SMC will review the available safety data to determine if the study should proceed as planned. If none of the events described above have been observed, dose escalation will proceed according to the protocol requirements.

9.7 Individual Dose Limiting Toxicity

- Any single grade 3 AE or Lab abnormality
- Fecal occult blood remains positive for 3 consecutive stool samples, hemorrhoids are excluded
- Evidence of frank hematemesis or hematochezia/melena of any duration
- Any clinical signs or symptoms the PI has determined is unsafe to administer IP

If an individual subject in a cohort reaches dose limit toxicity as determined by any of the above criteria, the subject will not receive any additional doses, and will be withdrawn from the study. All subjects withdrawn from the study will undergo routine follow up safety monitoring.

9.8 Safety Oversight (Safety Review Committee, Independent Safety Monitor plus Safety Monitoring Committee)

9.8.1 Independent Safety Monitor (ISM)

The ISM is a physician located near each respective investigator site with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This ISM is identified by the investigator site and approved by DMID. The ISM will review all SAEs as submitted by the clinical site and other AEs as needed and provide an independent written assessment to DMID for each SAE. The study site will have an ISM with experience in infectious diseases or internal medicine.

9.8.2 Safety Monitoring Committee (SMC)

This clinical trial will utilize an SMC, which is an independent group of experts that advises DMID. The primary responsibility of the SMC is to monitor subject safety. The SMC is external to DMID and composed of at least three voting members. The SMC will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. Its activities will be delineated in a SMC charter that will describe membership, responsibilities, and the scope and frequency of data reviews. The SMC will operate on a conflict-free basis independently of the study team. DMID or the SMC may convene ad hoc meetings of the SMC according to protocol criteria or if there are concerns that arise during the study. All reviews by the SMC will be performed with blinded data, unless otherwise requested by the SMC chair. If unblinded data are requested, the SMC will review the unblinded data in a closed session.

The SMC review of all safety and PK data after completion of each cohort. The SMC will also be consulted on an *ad hoc* basis if halting criteria are met, when recommendations are sought for clinical findings, and to recommend dose escalation.

10 CLINICAL MONITORING

All clinical monitoring activities will be conducted in accordance with ICH/GCP, applicable Parts in Title 21/45 of the CFR, and DMID requirements for the clinical monitoring of the study conducted under Contract No. Phase 1 DMID HHSN272201100030C.

10.1 Site Monitoring Plan

A Clinical Research Associate (CRA) will be responsible for the clinical monitoring of the study. This CRA will remain blinded throughout the study and will perform scheduled visits to verify that the clinical trial is being conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. A monitoring plan will be developed commensurate with the degree of potential risk to study subjects and the complexity of the study. Reports will be submitted to Emergent on monitoring activities. The site will provide direct access to all trial-related source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor and their designees, and inspection by local and regulatory authorities and their designees. The [redacted] Phase 1 Unit Clinical Research Coordinator will work closely with the CRA and will attempt to address the issues that are raised. The site PI is ultimately responsible for ensuring that the monitor's findings are addressed. The review of study records will be performed in a manner to ensure that subject confidentiality is maintained. There will also be an unblinded CRA responsible for product reconciliation as required throughout the study.

Monitoring procedures outlined in the Emergent -approved site monitoring plan will be followed in order to comply with Section 10.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Not applicable.

11.2 Sample Size Considerations

The study will enroll 8 subjects in each cohort for up to 5 cohorts. In each cohort, 6 subjects will be randomized to receive UV-4B and 2 will receive placebo. The number of subjects within each dose group was chosen based on historical experience with safety trials.

11.3 Planned Interim Data Review

After completion of the third cohort, a summary report will be provided to the SMC, including tables and listings of all data for each cohort. Recommendations from the SMC along with safety and PK data will be provided to the FDA after the completion of each cohort. All data will remain blinded. Initiation of dosing in subsequent cohorts will occur only after assessment of safety and plasma PK parameters from the previous cohort have been completed.

11.3.1 Safety Review

A blinded report with tables and listings including AEs will be provided to the SMC after each cohort.

11.3.2 Efficacy Review

Not applicable.

11.3.3 Pharmacokinetic Review

Pharmacokinetic parameters will be analyzed as described in Section 11.4.6. The PK data will be reviewed after each cohort.

11.4 Final Analysis Plan

11.4.1 Populations for Analysis

The safety population will be defined as all subjects who receive study product or placebo.

The PK population will consist of all subjects who receive study product, and have measurable values, and complete scheduled post-dose PK measurements without protocol

deviations, violations, or events thought to significantly affect the PK of the drug. In the case of a significant protocol deviation, PK data collected during the affected treatment period will be excluded from the analysis. Examples of significant protocol deviations or events include, but are not be limited to: vomiting following oral dosing occurring within 30 minutes, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing on the day of PK sampling.

11.4.2 Randomization and Stratification

Subject data will be analyzed according to treatment administered, as is standard for early clinical studies, due to the focus on safety and PK data. No stratification is planned for this study.

11.4.3 Procedures for Handling Missing, Unused, and Spurious Data

All available scheduled visit data will be included in data listings and tabulations. In addition, unscheduled visit data will be included in data listings. No imputation of missing values will be performed. Percentages of subjects with AEs or laboratory toxicities will be based on non-missing values. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

11.4.4 Statistical Plan

A formal statistical analysis plan for the analysis and presentation of data from this study will be finalized before database lock.

11.4.5 Safety

Safety variables will be tabulated and presented for all subjects in the safety population, grouped by treatment. Placebo subjects will be pooled into a single treatment group for analysis. Exposure to study product and reasons for discontinuation of study treatment will be tabulated.

Safety evaluation of AEs will be based on the incidence, intensity, and types of AEs. Changes in the physical examination findings, vital signs, and clinical laboratory results will be documented on an AE form. AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA®) AE coding system for purposes of summarization. All AEs occurring in the study will be listed in by-subject data listings. Treatment-emergent events will be tabulated, where treatment-emergent is defined as any AE that occurs after administration of the first dose of study product or that is already present prior to the first dose of study product and becomes more severe postdose. Treatment-emergent AEs will be tabulated by relatedness to study product and by maximum severity. Deaths, SAEs, and events resulting in study discontinuation will also be tabulated.

Observed values and change from baseline in clinical laboratory parameters will be summarized over the duration of the study. Shift tables will be produced for selected laboratory parameters. Observed values and changes in vital sign parameters and ECG intervals will be summarized over time in a similar fashion to laboratory parameters, and any abnormal values will be tabulated.

Summary statistics for continuous variables will include number of observations, mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized by the number and percent of subjects.

11.4.6 Pharmacokinetics

Pharmacokinetic parameters will be calculated by noncompartmental analysis using WinNonlin Professional® Version 5.2 or higher. All calculations for final plasma parameter analysis will be based on nominal sampling times. PK analysis will be performed at the completion of each cohort. The following PK parameters will be estimated:

- C_{max}
- t_{max}
- $AUC_{(0\text{-}last)}$
- $AUC_{(0\text{-}8)}$
- ($AUC_{(0\text{-}24)}$
- $AUC_{(0\text{-}inf)}$
- CL/F
- Vz/F
- $t_{1/2}$
- Accumulation ratio as defined by $AUC_{(0\text{-}8)}$ after the last dose divided by $AUC_{(0\text{-}8)}$ after the first dose

Plasma concentrations and plasma PK parameters will be summarized by cohort. PK parameters will also be presented in graphs as detailed in the SAP.

Dose proportionality of C_{max}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$ will be assessed graphically and statistically using the power model approach with the logarithm of PK parameters $AUC_{(0\text{-}inf)}$ and C_{max} as the dependent variables and the logarithm of the dose as the independent variable: ([$AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}last)}$, or C_{max}]=α*dose$^{\beta}$).

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The clinical site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. The PI and clinical site will permit trial-related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, DMID/NIAID, Emergent or their designee, including direct access to source data/documents (e.g., original medical records, laboratory reports, hospital documents, progress reports, signed ICFs in addition to eCRF's).

The data captured in source documents is transcribed into eCRFs by the study coordinator/staff. From this perspective, source documents are considered as origin for eCRF data and are subject to verification by the study monitor. Additional source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete and subject files and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Processes outlined in the DMID-approved Master Clinical Quality Management Plan (CQMP) will be implemented by the clinical site, [redacted] Phase 1 Unit, to ensure the integrity of the clinical data, safety and welfare of human subjects, and that the clinical trial is conducted in accordance with the approved protocol and with the applicable federal regulations and ICH guidelines. Findings from the CQMP activities will be submitted by written report to Emergent within five business days.

Emergent will audit the clinical site as needed during the course of the study.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The PI will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

14.2 Institutional Review Board

[redacted] IRB holds a current US Federal-wide Assurance issued by the Office of Human Research Protections.

Prior to initiation of the study, the site PI will submit the study protocol, sample ICF, and any other documents that pertain to subject information, recruitment materials such as advertisements, to IRB. The site PI must also submit any other information that may be requested to the IRB for review and approval. The site PI will request that the IRB provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. A letter confirming the approval must be forwarded to the CRA prior to initiation of this study. This letter will be forwarded to Emergent and DMID prior to the initiation of the study.

The PI must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The PI should notify the IRB of deviations from the protocol or SAEs occurring at the site, as well as other AE reports received from the [redacted] in accordance with local procedures.

The PI will be responsible for obtaining annual IRB approval or renewal throughout the duration of the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks of this therapy will be provided to the subjects. Consent forms describing in detail the study products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the PI will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the

opportunity to think about the study and discuss with others prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the study. A copy of the ICF will be given to the subjects for their records. The rights and welfare of the subjects will be protected according to 21 CFR 312.60.

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

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

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

14.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the PI, his/her staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

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

14.6 Study Discontinuation

The NIAID/DMID has the right to terminate/discontinue this study or an individual site's participation at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Incidence or severity of adverse events indicates a potential health hazard;
- Data recording is inaccurate or incomplete;
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

In the event that the study is discontinued, no further subjects will be dosed with UV-4B.

14.7 Future Use of Stored Specimens

Any plasma, blood, or urine left after all clinical laboratory testing is done will be discarded. Any plasma left after PK analysis will be stored at Emergent or designee bioanalytical laboratory and used for future research. A separately collected blood sample will be stored at Emergent or designated bioanalytical laboratory [redacted] At the completion of the protocol, the disposition of samples and data will be per Emergent instructions. Any loss or unanticipated destruction of samples or data will be reported to the IRB. In compliance with subject confidentiality and privacy act (e.g. HIPAA); no genetic testing, including pharmacogenomics, will be done on any stored specimens.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Management Responsibilities

Any source documents and laboratory reports must be reviewed by the clinical team and data management staff, who will ensure their accuracy and completeness. AEs must be graded based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* September 2007, as modified for this study and as appropriate for the administration of UV-4B

(Appendix II).

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

15.2 Data Capture Methods

Clinical data (including AEs and concomitant medications) will be entered into Medidata Rave, a 21 CFR Part 11-compliant electronic data capture (EDC) system managed by [redacted] The EDC system access is password protected. Access is granted to specific individuals based on the roles identified for the study. Clinical study sites enter the data into EDC and [redacted] monitors the data entry and accuracy of data entered. Data are validated through a query resolution process, comprising both automated and manual queries.

15.3 Types of Data

Data for this study will include all data for safety and PK deemed necessary for the analysis per the protocol, demographic data, concomitant medication, AE and medical history. Externally collected data are received and processed to present a complete dataset reconciled with data collected in the EDC.

15.4 Timing/Reports

Data collected at the bedside are available for review once it is entered into the EDC. Data are collected, reviewed, and queries are issued by [redacted] data management. The CRA will monitor the data and may also create queries for site clarification. AE data and concomitant medication data are coded by the MedDRA® and World Health Organization Drug (WHO DD) dictionaries respectively. Details regarding data collection, review, reconciliation, and reporting are discussed in the Data Management Plan.

15.5 Study Records Retention

Study documents should be retained for a minimum of 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 local regulations. No records will be destroyed without the written consent of Emergent. It is the responsibility of Emergent to inform the PI when these documents no longer need to be retained.

15.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or manual of procedures requirements. The noncompliance may be either on the part of the subject, the PI, or the study site staff. As a result of deviations, corrective actions and preventive actions are to be developed and documented by the site and implemented promptly with associated records provided to Emergent.

These practices are consistent with ICH E6:

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

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1 and 5.20.2.

It is the responsibility of the site to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol required activity. All deviations must be promptly reported in writing to Emergent.

16 PUBLICATION POLICY

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available as stipulated per the National Institute of Health Public Access Policy implements Division G, Title II, Section 218 of PL 110-161 (Consolidated Appropriations Act, 2008) which states:

SEC. 218. The Director of the National Institutes of Health shall require that all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine's Pub Med Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication: Provided, that the NIH shall implement the public access policy in a manner consistent with copyright law.

By signing the study protocol, the PI agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the authorities will be notified of the PI's name, address, qualifications, and extent of involvement.

If the PI or [redacted] is to be included as an author of a publication manuscript prepared by the Sponsor, the Sponsor will allow the PI or [redacted] 60 days for full review of the manuscript before publication.

17 LITERATURE REFERENCES

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, *et al.* The global distribution and burden of dengue. Nature. 2013;496:504-7.
2. Coniff R, Krol A. Acarbose: a review of US clinical experience. Clin Ther 1997; 19: 16-26.
3. Coniff RF, Shapiro JA, Seaton TB. Long-term efficacy and safety of acarbose in the treatment of obese subjects with non-insulin-dependent diabetes mellitus. Arch Intern Med 1994; 154: 2442-8.
4. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, *et al.* Dengue: a continuing global threat. Nat Rev Microbiol. 2010;8(12 Suppl):S7-16.
5. Simmons CP, Farrar JJ, Nguyen W, Wills B. Dengue. N Eng J Med. 2012;366:1423-32.

Supplements/Appendices

Supplements and Protocol Appendices

- Appendix I: Subject Flowdown
- Appendix II: UV-4B Toxicity Grading Criteria for Normal Human Subjects
- Appendix III: Iminosugar Clinical Signs
- Appendix IV: Schedule of Events
- Appendix V: General Treatment Plan for an Anaphylactic Reaction
- Appendix VI: Protocol Amendment(s)/Administrative Change(s)

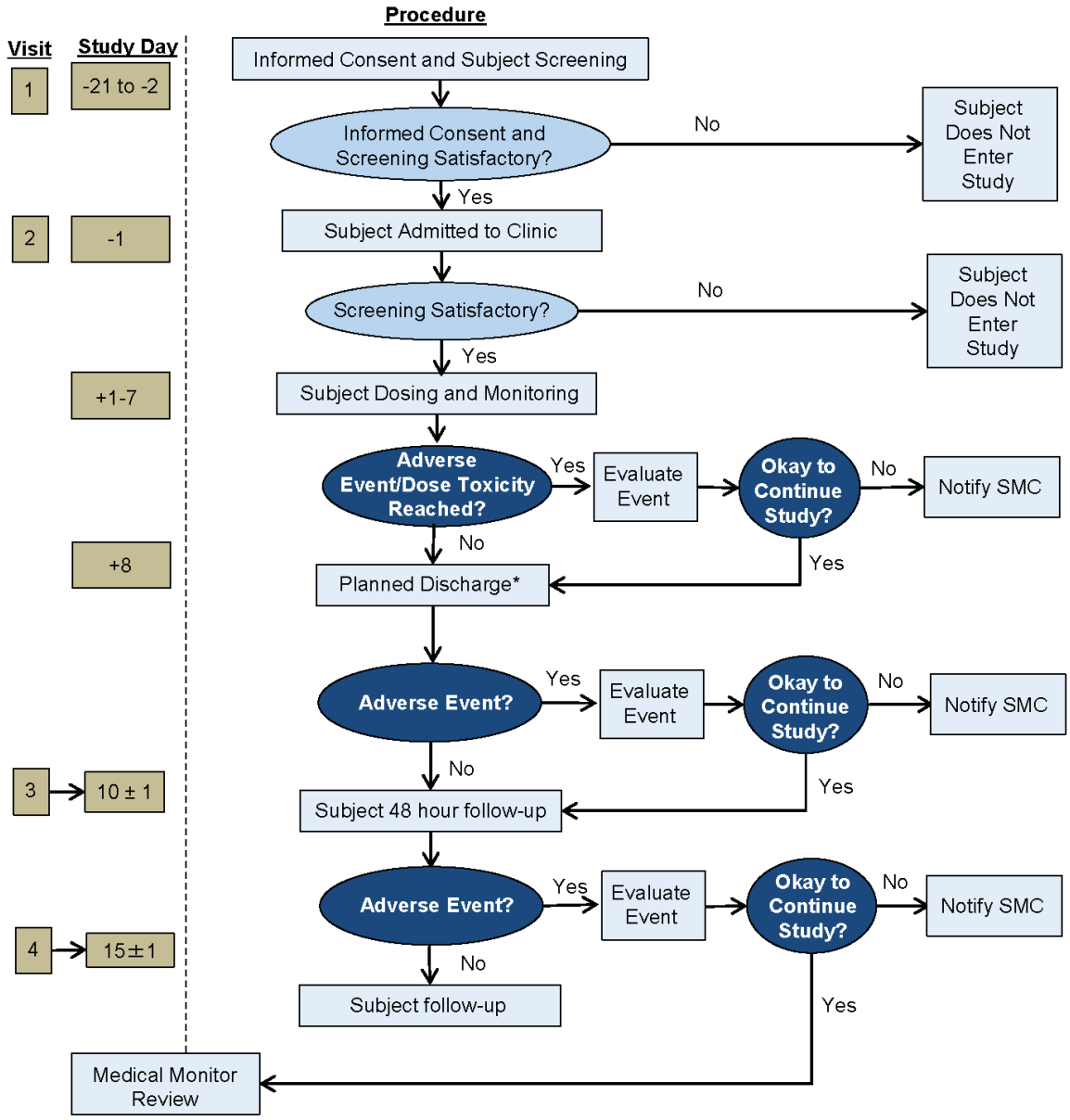
Related Documents

- Site Roster
- Manual of Procedures
- Repository Instructions
- Biosafety Precautions
- Laboratory Handling

Other Documents

- CRF copies
- Quality Management Plan
- Data Management Plan
- Clinical Monitoring Plan

APPENDIX I SUBJECT FLOWDOWN



APPENDIX II UV-4B TOXICITY GRADING CRITERIA FOR NORMAL HUMAN SUBJECTS

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)** (°F)**	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	>40 >104
Tachycardia – (beats per minute)	101 – 115	116 – 130	>130	Emergency room visit or hospitalization for arrhythmia
Bradycardia – (beats per minute)	50-54 if baseline >60 45-50 if baseline ≤ 60	45-49 if baseline >60 40-44 if baseline ≤ 60	<45 if baseline >60 <40 if baseline ≤ 60	Emergency room visit or hospitalization for arrhythmia
Hypertension (systolic) – mmHg	141 – 150	151 – 155	>155	Emergency room visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mmHg	91 – 95	96 – 100	>100	Emergency room visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	<80	Emergency room visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17-20	21-25	>25	Intubation

AE = adverse event; CRF = case report form

* Subject should be at rest for all vital sign measurements.

**Oral temperature; no recent hot or cold beverages or smoking

All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0 = absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No to mild interference with activity or 1 to 2 episodes/24 hours	Moderate interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 - 4 loose stools or < 400 gm/24 hours	5-6 stools or 400 – 800 gm/24 hours	7 or more watery stools or> 800gms/24 hours or requires outpatient IV hydration	Emergency room visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization

AE = adverse event; CRF = case report form

All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0 = absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical AE (as defined according to applicable regulations	No interference with activity	Some interference with activity, not requiring medical intervention	Prevents daily activity and requires medical intervention	Emergency room visit or hospitalization

AE = adverse event; CRF = case report form

All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0 = absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.

Serum	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium – hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	<125
Sodium – hypernatremia mEq/L	148 – 150	151 – 153	>154	Associated with seizures
Potassium – hyperkalemia mEq/L	5.3 – 5.4	5.5 – 5.6	>5.6	Associated with ECG changes
Potassium – hypokalemia mEq/L	3.0 – 3.5	2.5 – 2.9	2.0 – 2.4	≤1.9
Glucose – hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	<45
Glucose – hyperglycemia fasting mg/dL random mg/dL	 100 – 110 111– 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood urea nitrogen increase mg/dL	21 – 26	27 – 31	>31	Requires dialysis
Creatinine increase mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.8	7.5 – 7.9	7.0 – 7.4	<7.0
Calcium – hypercalcemia mg/dL	10.6 – 11.0	11.1 – 11.5	11.6 – 12.0	>12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.7	1.1 – 1.2	0.9 – 1.0	<0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	<1.6
Creatine phosphokinase – increase by factor	2.0 – 5.0 x ULN	5.1 – 10.0 x ULN	10.1 – 20 x ULN	>20 x ULN
Albumin – hypoalbuminemia g/dL	2.8 – 3.3	2.5 – 2.7	<2.5	--
Total protein – hypoproteinemia g/dL	5.5 – 5.9	5.0 – 5.4	<5.0	--
Alkaline phosphate – increase by factor	2.0 – 2.9 x ULN	3.0 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
Liver function tests – ALT, AST increase by factor	 1.1 – 2.5 x ULN	 2.6 – 5.0 x ULN	 5.1 – 10 x ULN	 >10 x ULN
Bilirubin – when accompanied by any increase in liver function test increase by factor	 1.1 – 1.25 x ULN	 1.26 – 1.5 x ULN	 1.51 – 1.75 x ULN	 >1.75 x ULN

Serum	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	>3.0 x ULN
Cholesterol increase mg/dL	201 – 210	211 – 225	>226	--
Pancreatic enzymes – amylase, and lipase – increase by factor	1.5 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 5.0 x ULN	>5.0 x ULN

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRF = case report form; ECG = electrocardiogram; ULN = upper limit of normal

Criteria are modified for this study based on reference values.

All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0 = absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) decrease - gm/dL	10.5-11.5	9.5-10.4	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) decrease - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase - cell/mm^3	10,901 –15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils decrease – cell/mm^3	1500-2000	1000-1,499	500-999	< 500
Eosinophils increase - cell/mm^3	650 – 1500	1501 – 5000	> 5000	Hypereosinophilic
PLT decrease - /mm^3	75,000 – 99,000	50,000 – 74,999	20,000 – 49,999	<20,000
PT – increase by factor	1.0 – 1.10 x ULN	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400-500	501-600	>600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation

PLT = platelet; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal; WBC = white blood cell count

Criteria are modified for this study based on reference values.

All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0= absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.

Urine	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – RBC per high power field (RBC/hpf)	1-10	11 – 50	> 50 and/or gross Blood	Hospitalization or packed red blood cells transfusion

AE = adverse event; CRF = case report form; hpf = high power field; RBC = red blood cell

Criteria are modified for this study based on reference values.

All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0 = absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.

APPENDIX III IMINOSUGAR CLINICAL SIGNS

Species	Drug	Finding (dose)[a]
Human	Zavesca®	Gastrointestinal diarrhea flatulence abdominal pain nausea vomiting bloating dyspepsia
		Metabolic and Nutritional Disorders weight decrease
		Central and Peripheral Nervous System headache tremor dizziness leg cramps par migraine
		Vision Disorders visual disturbance
		Musculoskeletal Disorders cramps
		Platelet, Bleeding, and Clotting Disorders thrombocytopenia
		Reproductive Disorders, Female menstrual disorder
	Glyset®	Gastrointestinal diarrhea flatulence abdominal pain ileus, including paralytic ileus nausea abdominal distension pneumatosis cystoides intestinalis
		Dermatologic skin rash
		Abnormal Laboratory Findings low serum iron reductions in hemoglobin or hematologic indices
	Precose®	Gastrointestinal

Species	Drug	Finding (dose)[a]
	(acarbose)	diarrhea flatulence abdominal pain and/or distension ileus, including paralytic ileus nausea loss of appetite clay-colored stools unusual bleeding (nose, mouth, vagina, or rectum pneumatosis cystoides intestinalis
		Abnormal Laboratory Findings low serum iron reductions in hemoglobin or hematologic indices
		Dermatologic purple or red pinpoint spots under the skin mild rash itching
Mouse	UV-4B	[redacted]
		[redacted]
		[redacted]
		[redacted]
		[redacted]
Rat		[redacted]
		[redacted]
		[redacted]
		[redacted]
		[redacted]

Species	Drug	Finding (dose)[a]
		[redacted]
Dog	UV-4B	[redacted]
		[redacted]
		[redacted]
		[redacted]
		[redacted]

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; FOB = functional observational battery; GALT = gut-associated lymphoid tissue; HGB = hemoglobin; HCT = hematocrit; RBC = red blood cell; WBC = white blood cell

[a] For mouse, rat, and dog studies, dose presented as mg/kg/dose, TID.

APPENDIX IV SCHEDULE OF EVENTS

Visit number	Visit 1 Screening period	Visit 2 Residential Period									Visit 3	Visit 4
		Admission to Clinic	Dosing (TID)							Discharge From Clinic	Follow-up	Follow-up
Activity\Day	Day -21 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10 ± 1	Day 15 ± 1
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Demographics	X											
Medical/surgical history	X											
Physical examination	X	X[(a)]	X (a)	X (a)	X (a)	X (a)	X (a)	X (a)	X (a)	X (a)	X (a)	X
Height and calculation of BMI	X											
Body weight	X	X							X	X		X
Vital signs (supine)	X	X	X (b),(c)	X (c)	X (c)	X (c)	X (c)	X (c)	X (c)	X	X	X
Orthostatic blood pressure & pulse rate	X	X	X (d)	X (d)	X (d)	X (d)	X (d)	X (d)	X (d)	X (d)		
Serology	X											
Urine [drugs of abuse & cotinine /alcohol test]	X	X										
Serum pregnancy test (e)	X	X										X
Urine pregnancy test (e)	X	X										
FSH (f)	X											

Visit number	Visit 1 Screening period	Visit 2 Residential Period								Visit 3	Visit 4
		Admission to Clinic	Dosing (TID)						Discharge From Clinic	Follow-up	Follow-up
Activity\Day	Day -21 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10 ± 1	Day 15 ± 1
Clinical chemistry, hematology, coagulation, & urinalysis	X	X		X	X	X	X	X	X	X	X	X
Hematology, clinical chemistry, & coagulation [subset]			X [g]									
Stool volume and frequency			X	X	X	X	X	X	X	X		
Fecal occult blood assessment	X		X [h]	X	X	X	X	X	X	X		X [h]
ECG [i]	X	X	X	X	X	X	X	X	X	X	X	X
Telemetry [i]		X	X	X	X	X	X	X	X			
Randomization			X [k]									
Administration of the investigational product			X	X	X	X	X	X	X			
PK blood sampling			X [l]	X [m]	X [m]	X [m]	X [m]	X [m]	X [n]	X [n]	X [n]	
Vomitus Occult [p] blood assessment			X	X	X	X	X	X	X	X	X	X
Sham Dosing		X										
Check-in to the clinic		X										
Discharge from the clinic										X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
AEs			X	X	X	X	X	X	X	X	X	X

Visit number	Visit 1 Screening period	Visit 2 Residential Period									Visit 3	Visit 4
		Admission to Clinic	Dosing (TID)							Discharge From Clinic	Follow-up	Follow-up
Activity\Day	Day -21 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10 ± 1	Day 15 ± 1

(a) Abbreviated physical examination (general appearance, heart, lungs, skin and abdomen) Day -1, Day 8 and Day 10, and brief neurological examination (mental status, motor system, and sensory system) will be done Day -1 through Day 8 and Day 10. In addition, brief physical examinations focused on the examination of skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and cutaneous) will be performed Days -1 through 8, and Day 10 (including a Day 1 examination prior to the first dose and 30 minutes after the 1st dose). Symptom directed/targeted physical examinations will be done at other study time points based on subject symptoms.

(b) Vital signs (blood pressure and pulse rate including oral temperature and respiratory rate) taken after 10 minutes supine rest; should be taken after ECG recordings (1 hour window for pre-dose procedures).

(c) At pre-dose, and hourly up until 2 hours after the third dose of the investigational product per day.

(d) Blood pressure and pulse rate taken after 2 minutes in standing position. At pre-dose, and hourly up until 2 hours after the third dose of the investigational product per day.

(e) Females only.

(f) Postmenopausal females only.

(g) A subset of hematology (PLT count), serum chemistry (AST, ALT), and coagulation (INR, PT, aPTT) assessments will be collected prior to the first dose only.

(h) Fecal occult assessments will be performed on Day 1 starting approximately 6 hours post first dose on every stool sample. On Day 15, fecal occult assessment may be performed as per discretion of the PI, and, if positive, followed until resolution.

(i) Triplicate 12-lead ECGs at baseline (Day 1 pre-dose); single 12-lead ECGs obtained at the same time each day for all residential days. [ECGs will be repeated for confirmation of any stopping criteria and at the PI's discretion].

(j) Telemetry for at least 4 hours on Day -1 and starting at -0.5 hours prior to the first dose (Day 1) and continuously through 4 hours post the first dose. Starting at 0.5 hours prior to the 3rd dose on Day 7 continuously through 4 hours post dose. (PI discretion based on ECG results)

(k) Pre-dose on Day 1

(l) Blood samples for PK analysis will be collected at pre-dose (0 hour) and after the first dose at 0.25 (±5 min), 0.5 (±5 min), 1 (±10 min), 1.5 (±10 min), 2 (±10 min), 2.5 (±15 min), 3 (±15 min), 5 (±30 min), 6 (±30 min), 8 (±30 min) hours (8 hour sample to be collected immediately before the second dose),

(m) One trough sample daily within fifteen (15) minutes before the first dose

(n) Immediately (within fifteen minutes) before the final dose, and at 0.25 (±5 min), 0.5 (±5 min), 1 (±10 min), 1.5 (±10 min), 2 (±10 min), 2.5 (±15 min), 3 (±15 min), 5 (±30min), 6 (±30 min), 8 (±30 min), 10 (±30 min), 12 (±30 min), and 14 (±30 min) hours after the final dose;

(o) One sample.

(p) Vomitus occult assessment will be done on all vomitus

APPENDIX V GENERAL TREATMENT PLAN FOR AN ANAPHYLACTIC REACTION

[redacted] has medical emergency drills for study providers which includes emergency assessment and management of anaphylaxis.

General: Call 911 regardless of on-scene care and patient response; Anaphylaxis requires close follow-up in an emergency room setting and if complicated, investigation and follow-up by an allergy specialist.

Assess patients: Use the Airway, Breathing, Circulation, Disability, and Exposure (ABCDE*) approach to assessment and response.

Call clinical trials unit supervisor, page the study physician and ask for help early.

Patients having an anaphylactic reaction require the following:

Establish airway by position, by using an Oropharyngeal Airway (OPA) or intubation.

1. High flow oxygen monitored using pulse oximetry:
2. Intravenous (IV) fluid challenge (weight based)
3. Intramuscular (IM) epinephrine 1:1000 with massage at injection sites.
4. Blood pressure monitoring
5. ECG
6. Epinephrine *(give IM unless experienced with IV dosing)*
7. IM doses of 1:1000 epinephrine (repeat after 5 min if no better)
    - Adult 500 micrograms IM (0.5 mL)
8. IV epinephrine to be given only by experienced specialists
9. Titrate: Adults 50 micrograms;

Further management:

Transport by advanced life support (ALS) to local emergency department. All anaphylaxis cases require evaluation. Medical Monitors will be paged.

APPENDIX VI PROTOCOL AMENDMENT(S)/ADMINISTRATIVE CHANGE(S)

PROTOCOL AMENDMENT 3

Background:

The protocol was amended for administrative reasons. None of the changes will affect the safety of subjects or the scientific integrity of the trial.

Modifications to the Protocol:

General Revisions:

- Administrative changes to update the contact details of the Emergent Medical Monitor, add contact details for the Emergent Clinical Project Specialist, and modify the sponsor signatories.

Sectional Revisions:

Location[a]	Old Text	New Text	Rationale
General Changes	-	The protocol header, title page, and Sponsor's signature page were updated to reflect protocol amendment 3 (version 4) and its issue date. An Amendment 3 summary of changes was incorporated in Appendix VI.	Administrative changes related to the protocol format
Sponsor's Signature Page (p. 3)	[redacted] Senior Manager, Clinical Operations [redacted] Principal Statistician [redacted] Senior Manager, Regulatory Affairs [Signatories with dates]	[redacted] Clinical Project Specialist II, Clinical Operations [redacted] Principal Statistician [redacted] Senior Manager, Regulatory Affairs [Signatories with dates]	Administrative changes in sponsor personnel
1 Key Roles (p. 17)	**Emergent Medical Monitor:** [redacted]	**Emergent Medical Monitor:** [redacted] **Emergent Clinical Project Specialist:** [redacted]	Administrative changes to update contact details for the Emergent Medical Monitor and add the Emergent Clinical Project Specialist

Location[a]	Old Text	New Text	Rationale
		[redacted]	
5.3.5 Emergency Unblinding (p. 48-49, paragraph 2)	**Emergent Medical Monitor:** [redacted]	**Emergent Medical Monitor:** [redacted]	Administrative change in contact details

[a]Pagination reflects content placement of the "Old Text" in Protocol Amendment 2, version 3, dated 21 November 2016.

PROTOCOL AMENDMENT 2

Background:

The protocol is being amended to facilitate subject enrollment through minor modification of eligibility criteria and the addition of a second study site and Principal Investigator. Clarifying text and other administrative changes have also been incorporated throughout related primarily to the addition of the second study site. While the changes (listed below) do involve, among other aspects, the type and timing of safety assessments and blood samples drawn, none of the changes will affect the safety of subjects or the scientific integrity of the trial.

Modifications to the Protocol:

General Revisions:

- Change in inclusion criterion #3 for the type of confirmatory pregnancy testing required before study enrollment: negative serum and urine tests at Screening and on Day -1 (previously it was a negative urine test at Screening and negative serum test on Day -1)
- Change in pregnancy testing: serum pregnancy test added at screening and urine pregnancy test added at Day -1
- Change in inclusion criterion #4 to allow inclusion of women with documented irreversible surgical sterilization by tubal ligation or occlusion
- Change in inclusion criterion #8 to ensure male subjects are not donating sperm from the first day of dosing until 3 months after the last dose of UV-4B
- Change in inclusion criterion #9 to require exercise restriction starting 4 days prior to dosing on Day 1 (to align with existing language under Section 8.3 Diet, Exercise, and Study Restrictions) and otherwise align the text under Section 8.3 with this inclusion criterion for the restriction to also apply at least 96 hours prior to the follow-up visits
- Change in inclusion criterion #10 to require a negative test result for cotinine (instead of specifying cotinine <500 ng/mL) for confirmation of current nonsmoking status
- Change in exclusion criterion #5 to exclude subjects with Grade 2 or higher proteinuria (previously higher than Grade 2 was exclusionary)
- Change in exclusion criterion #6 to specify the criterion refers to vital signs taken while supine and to require the exclusion of Grade 2 or higher vital sign abnormalities at check-in Day -1
- Change in exclusion criterion #8 remove reference to automated reading by the ECG machine and otherwise within the text clarify the PI must review all ECG findings

- Change in exclusion criterion #9 to 1) modify the exclusionary laboratory tests at baseline Day -1 (same exclusionary labs as at screening changed to any test results of Grade 2 or higher against the toxicity grading scale), 2) remove a requirement for the PI to seek the approval of the Emergent Medical Monitor for the enrollment of subjects having values for specified tests at screening falling outside the normal range, and 3) clarify that the urine protein test must be repeated when urine spermatozoa are present
- Addition of language to specify screen failures may be reconsented and rescreened under certain circumstances
- Addition of language that baseline clinical laboratory test results must be promptly reviewed by the PI, including for exclusionary test results of Grade 2 or higher against the toxicity grading scale
- Correction under Section 8.2.1 and schedule of assessments for the timing of clinical laboratory assessments, including fecal occult blood and stool volume and frequency
- Clarification of the fecal occult blood criterion mandating study withdrawal as an individual dose-limiting toxicity: positive results for fecal occult blood should be observed for three consecutive stool samples (as opposed to three days)
- Elimination of quantitative platelet function testing with PFA100
- Increase in the PK blood sample collection volume at each time point from 2 mL to 3 mL, resulting in a total collection volume of 93 mL (from 62 mL)
- Modification in telemetry: 12 leads to 5 leads
- Addition of a second study site and Principal Investigator
- Modification of the randomization plan to specify 1) the randomization schedule is prepared by the [redacted] unblinded statistician, 2) envelopes containing the randomization schedule will be provided to the sites before the start of dosing , 3) having two back-up subjects per cohort be available in case of subject withdrawal prior to dosing is optional, and 4) details on the randomization procedure are provided in the Pharmacy Manual
- Reference to a central laboratory removed, a local laboratory specified for the second site, and the approximate turnaround time for laboratory reports updated (approximately 36 hours after sample collection to the same day as sample collection)
- Revision of the toxicity grading scale for general clarification (e.g., addition of missing lab test units and/or directionality of the lab result), standardization and correction of table footnotes (including how/when to report graded values as AEs), and minor typographical correction
- Text change to accommodate different treatment options and different laboratory tests available at the sites for hypersensitivity reactions

- Correction of the text on UV-4B preparation, to remove un-necessary details on type and use of materials
- Clarification of assessments for AE severity and AE toxicity grading and definition of treatment-emergent AE
- Clarification for the reporting as AEs of any medical condition or graded laboratory value in relationship to the timing of onset with respect to taking the first dose of study drug: not considered an AE before ingestion of the first dose but considered an AE after ingestion of the first dose or if deteriorating from the baseline condition
- Administrative changes, including reformatting of the protocol according to Emergent's latest style template (involving a change in appendix numbering from alphabetic to Roman) and minor modifications to text to improve clarity, simplify the text, or correct typographical or other errors

Sectional Revisions:

Location[a]	Old Text	New Text	Rationale
General Changes	-	The protocol was reformatted using Emergent's latest style template, requiring a change in appendix numbering (alphabetic to Roman). Cosmetic changes to appendix numbering are not individually listed in this change summary unless associated with other, non-cosmetic text change(s). The protocol header, title page, and Sponsor's signature page were updated to reflect protocol amendment 2 (version 3) and its issue date. An Amendment 2 summary of changes was incorporated in Appendix F (now Appendix VI).	Administrative changes related to the protocol format
Title Page	Principal Investigator: [redacted]	Principal Investigator(s): [redacted]	Second site and Principal Investigator added to facilitate study enrollment
Sponsor Signature Page (p. 3)	[redacted] Director, Biostatistics [redacted] Senior Manager, Regulatory Affairs [Signatory with date]	[redacted] Principal Statistician [redacted] Senior Manager, Regulatory Affairs [redacted] Senior Director, Product Development [Signatories with dates]	Administrative change to replace and add Sponsor signatories
Investigator Signature Page (p. 4)	Site Investigator: Signed Date Name: [redacted]	Printed Name of Principal Investigator Signature of Investigator	Administrative change to accommodate signature collection from two investigators

Location[a]	Old Text	New Text	Rationale
	Title: Principal Investigator [Signatory with date]	Date [Signatory with date]	
List of Abbreviations (p. 10-11)	Select abbreviations: PFA100 System for analyzing platelet function	Select abbreviations: <deleted> WHO DD World Health Organization Drug Dictionary	Removal of quantitative platelet function testing with PFA100 in light of other platelet and bleeding assessments being performed (see under Sections 8.1 and 8.2.1); and addition of WHO DD for alignment with text
Protocol Summary (p. 12)	Number of Sites: One Phase 1 study site	Number of sites: Up to two Phase 1 study sites	Second study site added to facilitate study enrollment
1. Key Roles (p. 16)	**Principal Investigator:** [redacted]	**Principal Investigators:** [redacted] [redacted]	Second site and Principal Investigator added to facilitate study enrollment, and administrative change to correct the Dallas site address

Location[a]	Old Text	New Text	Rationale
1. Key Roles (p. 17)	**DMID Pharmacovigilance Group:** Clinical Research Operations and Management Support (CROMS) [redacted]	**Pharmacovigilance:** Emergent Global Pharmacovigilance Department [redacted]	Administrative change to correct the name and contact details of the group supplying pharmacovigilance support for the study
1. Key Roles (p. 17)	**Clinical Laboratory:** [redacted]	**Clinical Laboratories:** [redacted]	Administrative change to specify a local laboratory for each site, by adding the clinical laboratory for Madison
1. Key Roles (p. 17-18)	**Investigator Site:** [redacted]	**Investigator Sites:** [redacted]	Second study site added to facilitate study enrollment, and administrative change to correct the Dallas site address

Location[a]	Old Text	New Text	Rationale
		[redacted]	
1. Key Roles (p. 18)	[redacted]	[redacted]	Administrative change (address correction)
2.3.1 Potential Risks (Second paragraph of Item 3 under paragraph 2) (p. 35)	The changes in PLT count and aPTT are unlikely to be of concern in healthy subjects. The lymphoid depletion is unlikely to be of clinical concern over a short dosing period; however, the possibility that it is a manifestation of cytokine production, for example stimulation of Interleukin 4, needs to be considered. In this MAD study, careful monitoring of PLT count and coagulation parameters (aPTT, prothrombin time [PT]) as well as lymphocytes has been implemented. In addition, brief physical examinations focused on the examination of skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and cutaneous), as well as queries for gingival bleeding during dental care, will be performed daily.	The changes in PLT count and aPTT are unlikely to be of concern in healthy subjects. The lymphoid depletion is unlikely to be of clinical concern over a short dosing period; however, the possibility that it is a manifestation of cytokine production, for example stimulation of Interleukin 4, needs to be considered. In this MAD study, careful monitoring of PLT count and coagulation parameters (aPTT, prothrombin time [PT] and international normalized ratio [INR]) as well as lymphocytes has been implemented. In addition, brief physical examinations focused on the examination of skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and cutaneous), as well as queries for gingival bleeding during dental care, will be performed daily.	Text correction to specify that INR is also being monitored in this study as part of the coagulation panel
4. Study Design (last sentence of paragraph 1) (p. 39)	The study product and placebo will be masked so that the subjects and the site personnel including the PI will be blinded to the treatment assignment.	The study product and placebo will be masked so that the subjects and the site personnel including the PI will be blinded to the treatment assignment. Recruitment will occur at up to two investigational sites	Clarification that recruitment will occur at up to two sites
5 Study Enrollment	Only subjects who meet all of the inclusion and none of	Only subjects who meet all of the inclusion and none of	To add that screen

Location[a]	Old Text	New Text	Rationale
and Withdrawal (p. 40)	the exclusion criteria prior to dosing will be eligible for enrollment into this study. No exemptions are granted on inclusion/exclusion criteria in DMID-sponsored studies.	the exclusion criteria prior to dosing will be eligible for enrollment into this study. No exemptions are granted on inclusion/exclusion criteria in DMID-sponsored studies. Subjects who are screen failures due to transient conditions are permitted to be rescreened one time. In the event that the subject is rescreened for trial participation, a new informed consent form (ICF) must be signed.	failures may be reconsented and rescreening may occur in accordance with the NIH Healthy Volunteer Policy
5.1 Subject Inclusion Criteria (Criterion #3) (p. 40)	3. Females must have a negative urine pregnancy test at screening and serum pregnancy test on admission to the unit, must not be lactating, confirmed at screening and at checkin;	3. Females must have negative serum and urine pregnancy tests at screening and on admission to the unit, and must not be lactating, confirmed at screening and at check-in;	A serum pregnancy test was added to the screening visit and urine pregnancy test was added to Day -1; at screening and Day -1, the serum and urine test results are used to determine study eligibility
5.1 Subject Inclusion Criteria (Criterion #4, bullet 2) (p. 40)	4. Females must meet one of the following criteria at screening: • . . . .; • Have documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation or occlusion or;	4. Females must meet one of the following criteria at screening: • . . . .; • Have documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or tubal ligation or occlusion or;	To allow additional reliable form of birth control by inclusion of women with documented irreversible surgical sterilization by tubal ligation or occlusion
5.1 Subject Inclusion Criteria (Criterion #8) (p. 40-41)	8. Healthy male subjects should be willing to use barrier contraception during sexual intercourse, e.g., condoms, even if they have had a vasectomy, their partners are postmenopausal, surgically sterile, or are using accepted contraceptive methods as defined in inclusion criterion 4 above, from the first day of dosing until 3 months after the last dose of UV 4B;	8. Healthy male subjects must agree to not donate sperm from the first day of dosing until 3 months after the last dose of UV-4B and be willing to use barrier contraception during sexual intercourse, e.g., condoms, even if they have had a vasectomy, their partners are postmenopausal, surgically sterile, or are using accepted contraceptive methods as defined in inclusion criterion	Addition that males must refrain from donating sperm during the specified interval, for consistency with guidance in the informed consent form

Location[a]	Old Text	New Text	Rationale
		4 above, from the first day of dosing until 3 months after the last dose of UV 4B;	
5.1 Subject Inclusion Criteria (Criterion #9) (p. 41)	9. Willing to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation: Strenuous exercise (i.e. long distance running > 5km/day, weight lifting, or any physical activity to which the subject is not accustomed) is to be avoided while confined to the Clinical Unit and for at least 96 hours prior to the follow-up visits;	9. Willing to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation: Strenuous exercise (i.e. long distance running > 5km/day, weight lifting, or any physical activity to which the subject is not accustomed) is to be avoided starting 96 hours (4 days) prior to dosing on Day 1 through the period of confinement in the Clinical Unit and for at least 96 hours prior to the follow-up visits;	Administrative change for consistency with text in Section 8.3, to require exercise restriction starting 4 days prior to dosing on Day 1
5.1 Subject Inclusion Criteria (Criterion #10) (p. 41)	10. Nonsmokers (refrained from any tobacco usage, including smokeless tobacco, nicotine patches, etc., for 3 month prior to the administration of the study product); subjects must have cotinine levels below those measured for smokers (<500 ng/mL).	10. Nonsmokers (refrained from any tobacco usage, including smokeless tobacco, nicotine patches, etc., for 3 month prior to the administration of the study product); subjects must have a negative test result for cotinine.	Administrative change to specify that the cotinine test result must be negative
5.2 Subject Exclusion Criteria (Criterion #5) (p. 41)	5. Proteinuria greater than 1+;	5. Proteinuria greater than or equal to 1+;	To exclude subjects with Grade 2 (1+) or higher proteinuria from the study
5.2 Subject Exclusion Criteria (Criterion #6) (p. 41)	6. Grade 1 or higher abnormalities in vital signs to include deviations in temperature, resting heart rate, blood pressure, and respiratory rate (see Appendix B). A second set of values were added to the toxicity table for subjects who present with asymptomatic bradycardia at baseline at time of screening (<60 bpm);	6. At screening, Grade 1 or higher abnormalities in supine vital signs to include deviations in temperature, resting heart rate, blood pressure, and respiratory rate (may be repeated once); at check-in (Day -1), Grade 2 or higher abnormalities in supine vital signs (see Appendix II). A second set of values were added to the toxicity table for subjects who present with asymptomatic bradycardia at baseline at time of screening (<60 bpm);	To clarify the vital signs must be taken in a supine position; clarify vital signs may be repeated once at screening; and add a requirement that Grade 2 or higher abnormalities are exclusionary at check-in Day -1
5.2 Subject Exclusion Criteria	8. Abnormal ECGs as read by the automated reader in the ECG machine , however; abnormal readings for the	8. Abnormal ECGs; however, abnormal readings for the following benign conditions will be acceptable for the	Administrative change to accommodate

Location[a]	Old Text	New Text	Rationale
(Criterion #8) (p. 41)	following benign conditions will be acceptable for the study: sinus bradycardia, sinus arrhythmia, early repolarization, nonspecific ST-T wave pattern or changes, right axis deviation (axis 100 degrees or less), first degree AV block (PR interval less than 210 ms), nonspecific intraventricular conduction delay (QRS less than 120 ms), indeterminate axis, and short PR interval (where no delta wave). If an abnormal ECG finding is previously recorded, medically insignificant, and attributed to other causes (i.e. body habitus), Principle Investigator (PI) may elect to enroll the subject.	study: sinus bradycardia, sinus arrhythmia, early repolarization, nonspecific ST-T wave pattern or changes, right axis deviation (axis 100 degrees or less), first degree AV block (PR interval less than 210ms), nonspecific intraventricular conduction delay (QRS less than 120ms), indeterminate axis, and short PR interval (where no delta wave). If an abnormal ECG finding is previously recorded, medically insignificant, and attributed to other causes (i.e. body habitus), Principal Investigator (PI) may elect to enroll the subject.	automated ECG readings or PI-read ECGs
5.2 Subject Exclusion Criteria (Criterion #9) (p. 42)	9. Laboratory values outside of normal range at screening or check in on Day -1; however, the following list are not considered exclusionary if values fall outside of normal range and are determined to be not clinically significant by the PI and approved by the Emergent Medical Monitor: <table of lab analytes including column of Hematology Values and table footnote as shown below> <u>Hematology Values</u> Low-Basophils Low-Eosinophils Lymphocytes Monocytes Neutrophils (Differential percentages, absolute values and RBC indices are not by themselves exclusionary; clinical correlation is recommended). *when urine spermatozoa are present, urine protein should be repeated if result is elevated.	9. At screening, laboratory values outside of the normal range; however, the following list of parameters (see below table) are not considered exclusionary if values fall outside of the normal range. At baseline/check-in (Day -1), values that are Grade 2 or higher based on the toxicity grading scale (Appendix II). <table of lab analytes: no change except as shown below under Hematology Values and table footnote> <u>Hematology Values</u> Low-Basophils Low-Eosinophils Lymphocytes Monocytes Neutrophils Differential percentages, absolute values and RBC indices *when urine spermatozoa are present, urine protein must be repeated if result is elevated.	Changes to facilitate study enrollment by 1) modification in the exclusionary laboratory tests at baseline Day -1 and 2) administrative changes in the language to clarify circumstances in which the PI may enroll subjects whose laboratory test results fall outside the normal range at screening,without having to seek prior sponsor approval; and clarification that the urine protein test must be repeated when urine spermatozoa are present

Location[a]	Old Text	New Text	Rationale
5.3.1. Randomization Procedures (p. 43-44)	A randomization schedule will be prepared and will be provided to the pharmacy staff at the clinic prior to the start of the study. Each cohort will consist of eight subjects randomized to 6 active/2 placebo administration. There will be two back-up subjects per cohort in the event of subject withdrawal prior to dosing. Following review of all eligibility criteria, subjects will be randomized and immediately dosed. Randomization numbers will be assigned to subjects sequentially. Table 4 indicates the planned randomization numbers for this study.	A randomization schedule will be prepared by the unblinded [redacted] statistician to randomly assign within each cohort six subjects to active treatment and two subjects to placebo. Enrollment is planned to occur at up to two sites. Envelopes containing the available randomization numbers and corresponding treatment assignments will be provided to the site(s) before the start of dosing. There may be two back-up subjects per cohort in the event of subject withdrawal prior to dosing. Following review of all eligibility criteria, subjects will be assigned the next available randomization number by the unblinded site pharmacist and immediately dosed. Table 4 indicates the planned randomization numbers for this study. Details on the randomization procedures are provided in the Pharmacy Manual.	In light of a second site added, clarification of the randomization plan, including that the back-up subjects are optional
6.2.2 UV-4B Preparation (p. 49)	At time of use, bulk drug substance will be removed from the container and weighed in the clinic pharmacy. An amount appropriate to the number of subjects being dosed and the dose to be administered will be solubilized in WFI in a Class A volumetric flask (appropriate size) with a Teflon cap. Gentle mixing by inversion will be used to solubilize the drug substance and generate a UV-4B stock solution. If required or convenient for the preparation of dilute dosing solutions, an intermediate dilution stock solution in WFI may be made. An appropriate volume of UV-4B stock solution will be removed using a syringe, and transferred into an oral dosing container. 10 mL of taste-masking agent (commercially obtained OraSweet-SF) will be added. If required, additional WFI will be added to increase the volume to 30 mL. The WFI and any glassware or plastic ware used for solubilization of the UV-4B, and dilution and dosing of the drug substance, will be single-use and sourced by the [redacted] Phase 1 unit. Detailed dose	At time of use, bulk drug substance will be removed from the container and weighed in the clinic pharmacy. An amount appropriate to the number of subjects being dosed and the dose to be administered will be solubilized in WFI. Gentle mixing by inversion will be used to solubilize the drug substance and generate a UV-4B stock solution. If required or convenient for the preparation of dilute dosing solutions, an intermediate dilution stock solution in WFI may be made. An appropriate volume of UV-4B stock solution will be removed using a syringe, and transferred into an oral dosing container. 10 mL of taste-masking agent (commercially obtained OraSweet-SF) will be added. If required, additional WFI will be added to increase the volume to 30 mL. The WFI and any glassware or plastic ware used for solubilization of the UV-4B and dilution and dosing of the drug substance will be sourced by the [redacted] Phase 1 unit. Detailed dose preparation	Clarification of procedures for the preparation of UV-4B for administration (eg, type of flask for solubilization and use of glassware or plastic ware)

Location[a]	Old Text	New Text	Rationale
	preparation instructions will be provided in the pharmacy manual.	instructions will be provided in the pharmacy manual.	
7.1 Day -21 to Day -2 (Screening) (Bullets 4 and 6) (p. 51)	• Record demographics including age, gender, ethnicity and race; • Obtain blood samples for clinical chemistry, hematology, coagulation tests, urinalysis, urine pregnancy test (if female), FSH (if post-menopausal), HIV, hepatitis B surface antigen, and hepatitis C antibody;	• Record demographics including date of birth, gender, ethnicity and race; • Obtain blood samples for clinical chemistry, hematology, coagulation tests, urinalysis, serum and urine pregnancy tests (if female), FSH (if post-menopausal), HIV, hepatitis B surface antigen, and hepatitis C antibody;	Correction to ensure accurate capture of subject age data; and to capture the serum pregnancy test added to the screening visit
7.2.1 Day -1 (Admission to Clinic; 24 hours prior to dosing) (Title heading, paragraph 1, and Bullets 2, 9 and 10) (p. 51-52)	7.2.1 Day -1 (Admission to Clinic; 24 hours prior to dosing) Eligible subjects will return to the clinic on Day -1 for the procedures listed below. All physical exams, blood tests and ECGs after subjects have been dosed are obtained at approximately the same time each morning (within 2 hours). • Confirm that subject adhered to fasting requirements of at least 3 hours before the first dosing; • Obtain serum pregnancy test (if female); • Obtain baseline clinical chemistry, hematology, coagulation (including quantitative platelet function test with PFA100), and urinalysis;	7.2.1 Day -1 (Admission to Clinic; approximately 24 hours prior to dosing) Eligible subjects will return to the clinic on Day -1 for the procedures listed below. • Obtain serum and urine pregnancy tests (if female); • Obtain baseline clinical chemistry, hematology, coagulation, and urinalysis. Must have no values that are Grade 2 or higher based on the toxicity grading scale in Appendix II;	Qualifier added to note clinic admission is performed "approximately" 24 hours prior to dosing; erroneous statement about dosing (on a non-dosing day) deleted (moved to Section 7.3.1); directive to ensure fasting before dosing (on a non-dosing day) deleted (moved to Section 7.3.1); urine pregnancy test added to Day -1; quantitative platelet function testing removed; and statement added that Grade 2 or higher lab values are exclusionary
7.3.1 Day 1 (bullets under	Prior to the administration of the first dose of study product, the following procedures will be performed:	Prior to the administration of the first dose of study product, the following procedures will be performed:	Text moved from Section 7.2.1 to

Location[a]	Old Text	New Text	Rationale
paragraph 1) (p. 53)	• Brief physical examination focused on the examination of skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and evidence of hematoma, ecchymosis or petechia), brief neurological examination (mental status, motor system, and sensory system); • Obtain vital signs (blood pressure, pulse rate, after being supine for 10 minutes, and orthostatic blood pressure and pulse rate (taken after 2 minutes in the standing position), respiratory rate and oral temperature; • Obtain a triplicate 12-lead ECG; • Obtain baseline blood sample for PK analysis (t=0), to be taken within 1 hour prior to first dose and quantitative PLT function test using PFA100; • Telemetry starting at -0.5 hours on Day 1 through at least 4 hours post the first dose; • Randomization	• Brief physical examination focused on the examination of skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and evidence of hematoma, ecchymosis or petechia), brief neurological examination (mental status, motor system, and sensory system); • Confirm that subject adhered to fasting requirements of at least 3 hours before the first dosing; • Obtain vital signs (blood pressure, pulse rate, after being supine for 10 minutes, and orthostatic blood pressure and pulse rate (taken after 2 minutes in the standing position), respiratory rate and oral temperature; • Obtain a triplicate 12-lead ECG; • Obtain baseline blood sample for PK analysis (t=0), to be taken within 1 hour prior to first dose; • Telemetry starting at -0.5 hours on Day 1 through at least 4 hours post the first dose; • Randomization	emphasize confirmation of fasted state before dosing; and removal of quantitative platelet function testing
7.3.1 Day 1 (Paragraph 4) (p. 53-54)	<u>Following the administration of study product, the following procedures will be performed:</u> • Obtain clinical chemistry, hematology, and	<u>Following the administration of study product, the following procedures will be performed:</u> All physical exams, blood tests and ECGs after subjects have been dosed are obtained at approximately the same	Statement added (moved from Section 7.2.1) to clarify expectations for the relative timing of

Location[a]	Old Text	New Text	Rationale
	coagulation; • Obtain blood samples for PK analysis at 0.25 (±5 min), 0.5 (±5 min), 1 (±10 min), 1.5 (±10 min), 2 (±10 min), 2.5 (±15 min), 3 (±15 min), 5 (±30 min), 6 (±30 min), 8 (±30 min) hours (8 hour sample to be collected immediately before the second dose). • Obtain vital signs (blood pressure and pulse rate including oral temperature and respiratory rate) at 1, 2, 3, 4, 5, 6 and 7 hours (±15 minutes), after each administration of the study product (after ECG recording). Vital signs should be taken after being supine for 10 minutes, and orthostatic blood pressure and pulse rate (taken after 2 minutes in the standing position); • Telemetry through at least 4 hours post first dose; • Obtain fecal occult blood assessment starting approximately 6 hours post first dose on every stool sample. Stool volume and frequency will be recorded; • Obtain occult blood on all vomitus; • Perform brief physical examination focused on the examination of skin and oropharyngeal mucosa for evidence of bleeding and/or bruising (oral [gums] and cutaneous) 30 minutes after the first dose;	time each morning (within 2 hours). • Obtain clinical chemistry, hematology, and coagulation; • Obtain blood samples for PK analysis at 0.25 (±5 min), 0.5 (±5 min), 1 (±10 min), 1.5 (±10 min), 2 (±10 min), 2.5 (±15 min), 3 (±15 min), 5 (±30 min), 6 (±30 min), 8 (±30 min) hours (8 hour sample to be collected immediately before the second dose). • Obtain vital signs (blood pressure and pulse rate including oral temperature and respiratory rate) at 1, 2, 3, 4, 5, 6 and 7 hours (±15 minutes), after each administration of the study product. Vital signs should be taken after being supine for 10 minutes, and orthostatic blood pressure and pulse rate (taken after 2 minutes in the standing position); • Telemetry through at least 4 hours post first dose; • Obtain fecal occult blood assessment starting approximately 6 hours post first dose on every stool sample. Stool volume and frequency will be recorded; • Obtain occult blood on all vomitus; • Perform brief physical examination focused on the examination of skin and oropharyngeal mucosa for	procedures; erroneous "(after ECG recording)" directive deleted for vital signs collection; and clarification added that the brief physical exam must be performed 30 (+ 15) minutes after the first dose

Location[a]	Old Text	New Text	Rationale
	• Review concomitant medication usage once daily; • Completed AE assessment (including SAEs) will be recorded on AE source forms throughout the study and placed in the subject's clinic records.	evidence of bleeding and/or bruising (oral [gums] and cutaneous) 30 (+ 15) minutes after the first dose; • Review concomitant medication usage once daily; • Completed AE assessment (including SAEs) will be recorded on AE source forms throughout the study and placed in the subject's clinic records.	
7.3.2 Day 2 through Day 7 (In-Clinic) (Last sentence of paragraph 1; first sentence of paragraph 2) (p. 54)	If a subject misses four (4) or less doses their continued participation in the study will be determined by the PI, the EV and NIAID medical monitors on a case by case basis. As per Section 7.2.1, all physical exams, blood tests and ECGs after subjects have been dosed are obtained at approximately the same time each morning after dosing (within 2 hours).	If a subject misses four (4) or less doses their continued participation in the study will be determined by the PI and the Emergent and NIAID medical monitors on a case by case basis. As per Section 7.3.1, all physical exams, blood tests and ECGs after subjects have been dosed are obtained at approximately the same time each morning after dosing (within 2 hours).	Typographical correction (EV to Emergent) and administrative change to section number, reflecting text moved from one section to another
7.3.3 Day 8 (Discharge from Clinic) (Bullet 3) (p. 55)	• Obtain clinical chemistry, hematology, coagulation (quantitative PLT function test with PFA100 will only be performed if changes are observed in coagulation values at the prior assessment), and urinalysis;	• Obtain clinical chemistry, hematology, coagulation, and urinalysis;	Removal of quantitative platelet function testing
7.3.4 Day 10 ± 1 (Outpatient Visit) (Bullet 3) (p. 56)	• Obtain clinical chemistry, hematology, coagulation (quantitative platelet function test with PFA100 will only be performed if changes at previous assessment), and urinalysis;	• Obtain clinical chemistry, hematology, coagulation, and urinalysis;	Removal of quantitative platelet function testing
7.4 Day 15 ±1 (Final Study Visit) (Bullet 3) (p. 56)	• Obtain clinical chemistry, hematology, coagulation (quantitative PLT function test with PFA100 will only be performed if changes are	• Obtain clinical chemistry, hematology, coagulation, and urinalysis;	Removal of quantitative platelet function testing

Location[a]	Old Text	New Text	Rationale
	observed at a prior assessment), and urinalysis;		
8.2.1 Clinical Laboratory Evaluations (Paragraph 1 and subheadings for Screening and Screening and check-in on Day -1 and Day -1 and Day 1 and Day -1, Days 1 through 8 and at follow up on Day 15 (±1)) (p. 58-59)	Laboratory assessments will be done at screening, check-in, Days 1 through 8, 10 (±1) and 15 (±1) unless otherwise noted at approximately the same time each day (within 10 minutes) . The following specific tests will be performed as per Appendix D. Screening: • Serology will include hepatitis B surface antigen, antibodies to hepatitis C, and antibodies to HIV. Screening and check-in on Day -1: • Urine: Toxicology screen to include at a minimum marijuana, cocaine, methamphetamine, opiates, phencyclidine, barbiturates, benzodiazepines, tricyclic antidepressants, methadone, and amphetamines. Cotinine level, pregnancy (screening only); urine alcohol levels; • Serum: Comprehensive metabolic profile (chemistry 17), complete hepatic panel to include LDH, γ-glutamyltransferase (GGT), AST, ALT and direct and indirect bilirubin. Serum fertility panel to include human chorionic gonadotropin (HCG) to exclude pregnancy (Day -1) and FSH (screening only) to confirm menopausal/amenorrheic status; • Hematologic/coagulation: Complete blood count with differential and quantitative PLTs. Coagulation studies will include international normalized ratio (INR), PT, and aPTT. Samples	Laboratory assessments will be done at screening, check-in (Day -1), Days 1 through 8, 10 (±1) and 15 (±1) unless otherwise noted at approximately the same time each day (within 10 minutes). The following specific tests will be performed as per Appendix IV. Screening: • Serology will include hepatitis B surface antigen, antibodies to hepatitis C, and antibodies to HIV. • Urine: Toxicology screen to include at a minimum marijuana, cocaine, methamphetamine, opiates, phencyclidine, barbiturates, benzodiazepines, tricyclic antidepressants, methadone, and amphetamines. Cotinine level, pregnancy; urine alcohol levels; and urinalysis with microscopic examination; • Serum: Comprehensive metabolic profile (chemistry 17), complete hepatic panel to include LDH, γ-glutamyltransferase (GGT), AST, ALT and direct and indirect bilirubin. Serum fertility panel to include human chorionic gonadotropin (HCG) to exclude pregnancy and FSH to confirm menopausal/amenorrheic status; • Hematologic/coagulation: Complete blood count with differential and quantitative PLTs. Coagulation studies will include international normalized ratio (INR), PT, and aPTT. Samples	Clarification that "check-in" is Day -1; clarification that Day -1 laboratory test results must be promptly reviewed when available, including that subjects having baseline clinical laboratory test values of Grade 2 or higher are study-ineligible; re-organization of clinical laboratory tests to clarify expectations by visit, incorporating the changes in serum/urine pregnancy testing and adding erroneously omitted tests; and removal of quantitative platelet function testing

Location[a]	Old Text	New Text	Rationale
	for select hematology (PLT count). • Day -1 and Day 1: • PLT function tests will be performed using industry standard PFA100 to support quantitative PLT assays obtained using automated coulter counter or equivalent industry standard prior to the first dose administration. Whole blood is to be drawn into a sodium citrate tube with a volume of at least 4.5 mL. The unprocessed whole blood sample is to be kept and transported at an ambient room temperature. • Day -1, Days 1 through 8 and at follow up on Day 15 (±1): • Fecal Occult Blood Assessment: At screening, subjects will be given a fecal occult blood card with instructions for use and return of card to the clinic on or before Day -1. This sample will serve as the pre-dose assessment in case the subject does not produce a stool sample prior to the first dose administration on Day 1. If any fecal occult blood test is positive during the study period, subject(s) will be evaluated and a test will be performed on all subsequent stool specimens until negative. If fecal occult blood remains positive (excluding for hemorrhoids) for 3 consecutive samples, subjects will be referred for a GI evaluation and will be withdrawn from the study.	for select hematology (PLT count); • Fecal Occult Blood Assessment: At screening, subjects will be given a fecal occult blood card with instructions for use and return of the card to the clinic on or before Day -1. This sample will serve as the pre-dose assessment. <u>Check-in Day -1:</u> • Urine: Toxicology screen to include at a minimum marijuana, cocaine, methamphetamine, opiates, phencyclidine, barbiturates, benzodiazepines, tricyclic antidepressants, methadone, and amphetamines. Cotinine level, pregnancy; urine alcohol levels; and urinalysis with microscopic examination; • Serum: Comprehensive metabolic profile (chemistry 17), complete hepatic panel to include LDH, GGT, AST, ALT and direct and indirect bilirubin, and pregnancy; • Hematologic/coagulation: Complete blood count with differential and quantitative PLTs. Coagulation studies will include INR, PT, and aPTT; • Fecal Occult Blood Assessment: If not already done, the returned screening test card will be assessed for evidence of fecal occult blood. The Day -1 laboratory test results (serum chemistry/hematology/urinalysis) are considered as	

Location[a]	Old Text	New Text	Rationale
	• Occult blood assessments will be done on all vomitus.	baseline. Laboratory reports will be available before dosing on Day 1 and must be promptly reviewed by the PI. Any subjects having one or more baseline laboratory test results meeting Grade 2 or higher criteria on the toxicity grading scale in Appendix II are ineligible for study participation. Days 1 through 8 and follow ups on Day 10 (±1) and Day 15 (±1): • Hematology, clinical chemistry, & coagulation: A subset of hematology (PLT count), serum chemistry (AST, ALT), and coagulation (INR, PT, aPTT) assessments will be collected prior to the first dose only on Day 1. Full clinical chemistry, hematology, coagulation, and urinalysis testing will be performed on Days 2 through 8 and follow ups on Day 10 (±1) and Day 15 (±1). • Fecal Occult Blood Assessment: Fecal occult blood assessments will be performed on Days 1 through 8 and Day 15. If any fecal occult blood test is positive during the study period, subject(s) will be evaluated and a test will be performed on all subsequent stool specimens until negative. If fecal occult blood remains positive (excluding for hemorrhoids) for 3 consecutive samples, subjects will be referred for a GI evaluation and will be withdrawn from the study. • Vomitus Occult Blood: Occult blood assessments will be done on all vomitus.	

<table>
<tr><th>Location[a]</th><th>Old Text</th><th>New Text</th><th>Rationale</th></tr>
<tr>
<td>8.2.1 Clinical Laboratory Evaluations
(last paragraph before Table 5 and Table 5 Safety Laboratory Tests)
(p. 59-60)</td>
<td>All laboratory assessments will be done by the clinical site's certified laboratory utilizing that clinical laboratory's normal ranges. Laboratory toxicity grading will be determined by use of the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007 and the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007 or as modified for this study and as appropriate for the administration of UV-4B (Appendix B).
<Table 5 Safety Laboratory Tests, including select columns for Chemistry and Coagulation analytes and table footnotes shown below>
<table><tr><th>Chemistry</th><th>Coagulation</th></tr><tr><td>Alkaline phosphatase
ALT[b]
AST[b]
Total bilirubin
. . .
. . .
Creatine phosphokinase[a], [b]
. . .
. . .
Amylase
Lipase</td><td>INR[b]
PT[b]
aPTT[b]
Platelet function [b]</td></tr><tr><td colspan="2">[a] If either lactate dehydrogenase or creatine phosphokinase is elevated, iso-enzyme levels will be determined using investigative assays.
[b] Samples for select hematology (PLT count), serum chemistry (AST and ALT), and coagulation</td></tr></table></td>
<td>All laboratory assessments will be done by the clinical site's certified laboratory. Laboratory toxicity grading will be determined by use of the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007 and the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007, as modified for this study and appropriate for the administration of UV-4B (Appendix II).
<Table 5 Safety Laboratory Tests: no change except as indicated below for Chemistry and Coagulation columns and the table footnotes>
<table><tr><th>Chemistry</th><th>Coagulation</th></tr><tr><td>Alkaline phosphatase
ALT[b]
AST[b]
Total bilirubin
. . .
. . .
Creatine phosphokinase[a]
. . .
. . .
Amylase
Lipase</td><td>INR[b]
PT[b]
aPTT[b]</td></tr><tr><td colspan="2">[a] If either lactate dehydrogenase or creatine phosphokinase is elevated (i.e., Grade 2 or higher, or otherwise deemed clinically significant by the PI), iso-enzyme levels will be determined using investigative assays.
[b] Samples for select hematology (PLT count),</td></tr></table></td>
<td>Clarification of text on laboratory evaluation, including that the grading criteria in Appendix B (now Appendix II) are already modified as appropriate for this study; removal of platelet function testing; and clarification of circumstances in which iso-enzyme levels must be determined</td>
</tr>
</table>

<table>
<tr><th>Location[a]</th><th>Old Text</th><th>New Text</th><th>Rationale</th></tr>
<tr><td></td><td>(INR, PT, aPTT, and quantitative platelet function test with PFA100) assessments will be collected on Day 1 prior to the first dose of study product. Quantitative platelet function test with PFA100 assessments will also be collected on subsequent days (if changes are observed at the previous assessment).
[c] Differential should include absolute values</td><td>serum chemistry (AST and ALT), and coagulation (INR, PT, aPTT) assessments will be collected on Day 1 prior to the first dose of study product.
[c] Differential should include absolute values</td><td></td></tr>
<tr><td>8.2.2 Special Assays or Procedures
Table 6 Volume of blood to be drawn from each Subject
(p. 61)</td><td>Select table rows shown:
<table>
<tr><th>Type</th><th>Laboratory Test</th><th>Sample Volume (mL)</th><th>Number of Samples</th><th>Total Volume (mL)</th></tr>
<tr><td rowspan="2">Safety</td><td>aPTT, PT</td><td>2.7</td><td>1</td><td>2.7</td></tr>
<tr><td>Platelet function test</td><td>4.5</td><td>2</td><td>9[a]</td></tr>
<tr><td colspan="2">Pharmacokinetic</td><td>2</td><td>31</td><td>62</td></tr>
<tr><td colspan="2">Total</td><td>57.4</td><td>102</td><td>463.9</td></tr>
</table></td><td>Select table rows shown:
<table>
<tr><th>Type</th><th>Laboratory Test</th><th>Sample Volume (mL)</th><th>Number of Samples</th><th>Total Volume (mL)</th></tr>
<tr><td rowspan="2">Safety</td><td>aPTT, PT, INR</td><td>2.7</td><td>1</td><td>2.7</td></tr>
<tr><td colspan="4"><row deleted></td></tr>
<tr><td colspan="2">Pharmacokinetic</td><td>3</td><td>31</td><td>93</td></tr>
<tr><td colspan="2">Total</td><td>54.6</td><td>100</td><td>486.6</td></tr>
</table></td><td>Addition of INR to the coagulation test panel to correct an omission; removal of quantitative platelet function testing; and revision to collect 3 mL (not 2 mL) of blood for PK sampling to ensure sufficient plasma for testing and back-up sample</td></tr>
<tr><td>8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage
(Paragraph 1)
(p. 61)</td><td>The collected PK blood samples (2 mL) will be placed on ice after blood draw, and within 1 hour centrifuged at room temperature at approximately 3000 revolutions per minute for 15 minutes. Plasma will then be harvested and split into 4 aliquots of approximately 250 µL and stored frozen at -20°C until shipped.</td><td>The collected PK blood samples (3 mL) will be placed on ice after blood draw, and within 1 hour centrifuged at room temperature at approximately 3000 revolutions per minute for 15 minutes. Plasma will then be harvested and split into 3 aliquots of approximately 250 µL (any additional plasma placed in a fourth tube as a back-up sample) and stored frozen at -20°C until shipped.</td><td>Clarification of procedures to collect PK blood samples, requiring an additional 1 mL with each sample collection (total 3 mL) to ensure at least 3 aliquots of 250 µL plasma</td></tr>
<tr><td>8.3 Diet, Exercise, and Study Restrictions
(First sentence in</td><td>Enrolled subjects will be advised to abstain from strenuous exercise starting 96 hours (4 days) prior to dosing on Day 1 and continuing through the in-subject stay.</td><td>Enrolled subjects will be advised to abstain from strenuous exercise starting 96 hours (4 days) prior to dosing on Day 1 and continuing through the in-subject stay and for at least 96 hours prior to the follow-up</td><td>Administrative change for consistency with similar text in Section 5.1 (Inclusion Criterion</td></tr>
</table>

Location[a]	Old Text	New Text	Rationale
paragraph 1) (p. 62)		visits.	#9)
9.1.2. Vital Signs (last sentence) (p. 63)	Vital sign AEs will be graded according to toxicity grading criteria listed in Appendix B.	Vital sign values of Grade 1 or higher according to toxicity grading criteria listed in Appendix II will be reported as AEs.	Clarification that every Grade 1-4 vital sign finding must be reported as an AE.
9.1.3 Electrocardiograms (Paragraphs 2 and 3) (p. 63-64)	ECGs will be reviewed by PI or designee. The machine interpretation will be reviewed for accuracy and incorrect findings will be lined out on the tracing and not recorded in the case report form (CRF) (and correct reading substituted if necessary). ECGs with the following, even when reported by the ECG machine as "abnormal", will be considered acceptable for study and will not be considered abnormal for study purposes unless the PI or physician designee believes they represent a new medical condition when compared to baseline ECGs. In such cases an AE will be documented and the subject will be followed for safety evaluations as appropriate. The following pre-existing conditions identified at enrollment will not be considered adverse events: • sinus bradycardia; • sinus arrhythmia; • early repolarization; • nonspecific ST-T wave pattern or changes, mild or moderate right axis deviation; • first degree AV block (PR interval less than 210ms is acceptable); • nonspecific intraventricular conduction delay	All ECGs will be reviewed by the PI or designee. ECGs with the following readings will be considered acceptable for study and will not be considered abnormal for study purposes unless the PI or physician designee believes they represent a new medical condition when compared to baseline ECGs. In such cases an AE will be documented and the subject will be followed for safety evaluations as appropriate. The following pre-existing conditions identified at enrollment will not be considered adverse events: • sinus bradycardia; • sinus arrhythmia; • early repolarization; • nonspecific ST-T wave pattern or changes, mild or moderate right axis deviation; • first degree AV block (PR interval less than 210ms is acceptable); • nonspecific intraventricular conduction delay (QRS, or average of triplicate QRS; less than 120ms is acceptable); • short PR interval (where no delta wave), and	Administrative change to remove text on ECG machine readings, to emphasize all ECGs must be reviewed by the PI

Location[a]	Old Text	New Text	Rationale
	(QRS, or average of triplicate QRS; less than 120ms is acceptable); • short PR interval (where no delta wave), and indeterminate axis. Automated 12-lead ECG readings describe findings using a variety of terms based on the algorithm. As such, the above terms are not intended to be presented verbatim as machine readings vary slightly between different models and manufacturers. Only similar terms expressing identical concepts written on ECG tracing by the machine will be considered as equivalent to those mentioned above and acceptable for study. The Sponsor may review all or individual screening or Day -1 ECGs or may delegate to determine if meets intention of entry criteria goal of enrolling healthy normal study subjects.	indeterminate axis. The Sponsor may review all or individual screening or Day -1 ECGs or may delegate to determine if meets intention of entry criteria goal of enrolling healthy normal study subjects.	
9.1.4 Telemetry (First sentence in paragraph 1) (p. 65)	A 12-lead real-time telemetry ECG will be displayed for at least 4 hours on Day -1 while awake and again starting at -0.5 hours on Day 1 through at least 4 hours post initial-dose; starting at 0.5 hours prior to the 3rd dose on Day 7 continuously through 4 hours post dose.	A 5-lead real-time telemetry ECG will be displayed for at least 4 hours on Day -1 while awake and again starting at -0.5 hours on Day 1 through at least 4 hours post initial-dose; starting at 0.5 hours prior to the 3rd dose on Day 7 continuously through 4 hours post dose.	Administrative change (12-lead to 5-lead telemetry) to accommodate the equipment available at the Madison site
9.1.6 Clinical Laboratory Testing (p. 65-66)	Laboratory testing will be utilized to evaluate safety on an ongoing basis through the treatment and follow-up periods according to Section 8.2. Laboratory reports are sent from the clinical laboratory to the clinic daily and are filed in the subject charts. Any values outside of the laboratory defined range will be flagged as such by the clinical laboratory.	Laboratory testing will be utilized to evaluate safety on an ongoing basis through the treatment and follow-up periods according to Section 8.2. Laboratory reports from the local clinical laboratory will be provided to the clinic on the same day as sample collection and will be filed in the subjects' charts. Any values outside of the laboratory defined range will be flagged as such by the clinical laboratory.	Administrative change to clarify the turnaround time for laboratory reports from the local lab
9.1.7 Evaluation of Hypersensitivity Reactions	Laboratory abnormalities suggestive of HS reaction and requiring clinical corroboration include peripheral eosinophilia and urine eosinophils.	Laboratory abnormalities suggestive of HS reaction (e.g., peripheral eosinophilia) require clinical corroboration.	Administrative change to accommodate laboratory testing

Location[a]	Old Text	New Text	Rationale
(Last sentence of paragraph 1) (p.66)			differences
9.1.7 Evaluation of Hypersensitivity Reactions (Last sentence of paragraph 2; and paragraph 3) (p.66)	If HS reaction follows dosing, AE or SAE will be recorded in accordance with physical monitoring criteria or laboratory abnormalities noted in (Appendix B). The Phase 1 treatment facility is capable of managing all types of HS reactions from HS type I-IV with bedside epinephrine, diphenhydramine, terbutaline and albuterol nebulizers and oral and/or systemic steroids. [redacted] will follow their Standard Operating Procedures (SOPs) for treatment of HS reactions. Please see general anaphylaxis protocol (Appendix E).	If HS reaction follows dosing, AE or SAE will be recorded in accordance with physical monitoring criteria or laboratory abnormalities noted in Appendix II. The Phase 1 treatment facility is capable of managing all types of HS reactions from HS type I-IV (e.g., with bedside epinephrine, diphenhydramine, terbutaline and albuterol nebulizers and oral and/or systemic steroids). [redacted] will follow their Standard Operating Procedures (SOPs) for treatment of HS reactions. Please see general anaphylaxis protocol (Appendix V).	Typographical correction; and administrative change to the text to accommodate different options available for the treatment of HS reactions at the two study sites
9.2.1 Adverse Events (paragraph 3) (p.67)	Any medical condition that is present at the time that the subject is screened should be considered as baseline/pre-existing condition and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.	Any medical or laboratory condition that is present at the time that the subject is screened up through ingestion of the first dose should be considered as baseline/pre-existing condition and not reported as an AE. However, if it deteriorates at any time during the study after ingestion of the first dose, it should be recorded as an AE.	Clarification of AE reporting requirements with consideration for baseline/pre-existing medical conditions or baseline laboratory test results
9.2.1 Adverse Events (paragraphs 4 and 5) (p. 67)	All AEs must be graded for severity and relationship to study product. Adverse events will be graded according to the FDA Guidance for Industry*: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* and the *Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007* as modified for this study. For abnormalities not found in the toxicity tables, the PI will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one	All AEs must be assessed for severity and relationship to study product. The PI will make an assessment of severity for each AE and SAE reported during the study and will assign it to one of the following categories: Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities; Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities; Severe: An event that prevents normal everyday activities	Clarification that AEs are assessed for severity using a mild-moderate-severe scale and are also graded using Grades 1 through 4 according to the toxicity grading scale in Appendix B (now Appendix II). Furthermore, for AEs

Location[a]	Old Text	New Text	Rationale
	of the following categories: GRADE 1: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities; GRADE 2: An event that is sufficiently discomforting to interfere with normal everyday activities; GRADE 3: An event that prevents normal everyday activities;	In addition, all AEs will be graded (Grade 1 to 4) according to the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* and the *Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007* as modified for this study (Appendix II). For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0=absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.	or laboratory changes not addressed by the toxicity grading scale, a Grade of 0 shall be entered to indicate the grading does not apply.
9.2.3 Procedures to be following in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings (last sentence of paragraph 1) (p. 69)	The grading of abnormal clinical findings are based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* and *Division Of Microbiology And Infectious Diseases (DMID) Adult Toxicity Table November 2007* or as modified for this study (see Appendix B).	The grading of abnormal clinical findings are based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007* and *Division Of Microbiology And Infectious Diseases (DMID) Adult Toxicity Table November 2007* as modified for this study (see Appendix II).	Clarification that the toxicity grading criteria in Appendix B (now Appendix II) have already been modified as appropriate for this study
9.2.3 Procedures to be following in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings (first sentence of paragraph 2) (p. 69)	Grade 1 to 3 laboratory or clinical abnormalities will be reported and followed as an AE or SAE, as appropriate.	Any medical condition or graded laboratory value (according to Appendix II) after ingestion of the first dose or deterioration from the baseline condition will be reported and followed as an AE or, as appropriate, SAE.	Clarification that any change from baseline in medical condition or graded laboratory value after dosing qualifies for reporting as an AE, or if appropriate, SAE
9.7 Individual Dose Limiting Toxicity (Bullet 2) (p. 73)	• Fecal occult blood remains positive for 3 days, hemorrhoids are excluded	• Fecal occult blood remains positive for 3 consecutive stool samples, hemorrhoids are excluded	Clarification of the study withdrawal criterion

Location[a]	Old Text	New Text	Rationale
9.8.1 Independent Safety Monitor (ISM) (first sentence) (p. 73)	The ISM is a physician located near the investigator site with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion.	The ISM is a physician located near each respective investigator site with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion.	Clarification that each site has its own ISM
10.1 Site Monitoring Plan (first sentence in paragraph 1) (p. 75)	A Clinical Research Associate (CRA) will be responsible for the clinical monitoring of the study at the [redacted] Phase 1 Unit.	A Clinical Research Associate (CRA) will be responsible for the clinical monitoring of the study.	Change in text for applicability to a study with two study sites
11.4.3 Procedures for Handling Missing, Unused, and Spurious Data (First sentence) (p. 77)	All available scheduled data will be included in data listings and tabulations.	All available scheduled visit data will be included in data listings and tabulations.	Clarification of text
11.4.5 Safety (fifth sentence in paragraph 2) (p. 78)	Treatment-emergent events will be tabulated, where treatment-emergent is defined as any AE that occurs after administration of the first dose of study product.	Treatment-emergent events will be tabulated, where treatment-emergent is defined as any AE that occurs after administration of the first dose of study product or that is already present prior to the first dose of study product and becomes more severe postdose.	More complete definition of treatment-emergent adverse event
12 Source Documents and Access to Source Data/Documents (First sentence of paragraph 2) (p. 80)	Forms for use as source documents will be derived from the e-CRFs and will be provided by data management.	The data captured in source documents is transcribed into eCRFs by the study coordinator/staff. From this perspective, source documents are considered as origin for eCRF data and are subject to verification by the study monitor.	Clarification of text
15.2 Data Capture Methods (p. 85)	Clinical data (including AEs and concomitant medications) will be entered into a 21 CFR Part 11-compliant data management system provided by [redacted] The data system includes password protection	Clinical data (including AEs and concomitant medications) will be entered into Medidata Rave, a 21 CFR Part 11-compliant electronic data capture (EDC) system managed by [redacted] The EDC system access	Clarification of text

Location[a]	Old Text	New Text	Rationale
	and internal quality checks, such as automatic verification range checks, to identify data that appear to be out of the specified ranges. Programmed edit specifications identify discrepancies in the data that may are addressed by the site.	is password protected. Access is granted to specific individuals based on the roles identified for the study. Clinical study sites enter the data into EDC and [redacted] monitors the data entry and accuracy of data entered. Data are validated through a query resolution process, comprising both automated and manual queries.	
15.3 Types of Data (Last sentence) (p. 85)	Externally collected data are received and processed to present a complete dataset reconciled with data collected at in the EDC.	Externally collected data are received and processed to present a complete dataset reconciled with data collected in the EDC.	Typographical correction
15.4 Timing/Reports (p. 85-86)	Data collected at the bedside are available for review once it is entered into the EDC. Data are collected, reviewed, and queries are issued by data management (per the specifications in the Data Management Plan). The CRA will monitor the data and may also create queries for site clarification. AE data and concomitant medication data are coded by the MedDRA® and World Health Organization dictionaries. Any SAEs will also be reported through the appropriate processes identified in the Data Management Plan. After the data are deemed "clean" (i.e., no further changes are required), the CRA will approve the subjects' data by applying an esignature in the EDC system. Data will then be considered "frozen" and no new data can be entered into the system. The data will be reviewed by appropriate team members and the bioanalytical data will be received. Data for this study will include all data for safety and PK deemed necessary for the analysis per the protocol. Externally collected data will be received and processed to present a complete dataset reconciled with data collected at the bedside. The data will be moved to a status of "locked" and the data set transferred to the statistical programming team for creation of tables, figures, and listing review.	Data collected at the bedside are available for review once it is entered into the EDC. Data are collected, reviewed, and queries are issued by [redacted] data management. The CRA will monitor the data and may also create queries for site clarification. AE data and concomitant medication data are coded by the MedDRA® and World Health Organization Drug (WHO DD) dictionaries respectively. Details regarding data collection, review, reconciliation, and reporting are discussed in the Data Management Plan.	Text deleted because the information is not included in the DMP

Location[a]	Old Text	New Text	Rationale
Supplements/ Appendices (p. 89)	Supplements and Protocol Appendices Appendix A: Subject Flowdown Appendix B: UV-4B Toxicity Grading Criteria for Normal Human Subjects Appendix C: Iminosugar Clinical Signs Appendix D: Schedule of Events Appendix E: General Treatment Plan for an Anaphylactic Reaction	Supplements and Protocol Appendices Appendix I: Subject Flowdown Appendix II: UV-4B Toxicity Grading Criteria for Normal Human Subjects Appendix III: Iminosugar Clinical Signs Appendix IV: Schedule of Events Appendix V: General Treatment Plan for an Anaphylactic Reaction Appendix VI: Protocol Amendment(s)/Administrative Change(s)	Administrative changes to reflect the new numbering scheme for the appendices and to add a reference to Appendix F (now Appendix VI) for completeness
Appendix B (now Appendix II): UV-4B Toxicity Grading Criteria for Normal Human Subjects (all subtables) (p. 91-95)	Table rows, footnote markers, footnotes, and defined abbreviations in each subtable, as indicated: <u>Vital Signs Subtable</u> Hypotension (systolic) – mmHg 85 – 89 80 – 84*** <80 Emergency room visit or hospitalization for hypotensive shock * Subject should be at rest for all vital sign measurements. **Oral temperature; no recent hot or cold beverages or smoking <u>Systemic (General) Subtables</u>	Table rows, footnote markers, footnotes, and defined abbreviations in each subtable, as indicated: <u>Vital Signs Subtable</u> Hypotension (systolic) – mmHg 85 – 89 80 – 84 <80 Emergency room visit or hospitalization for hypotensive shock AE = adverse event; CRF = case report form * Subject should be at rest for all vital sign measurements. **Oral temperature; no recent hot or cold beverages or smoking All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0 = absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply. <u>Systemic (General) Subtables</u>	Administrative changes (e.g., addition of missing lab test units and/or directionality of lab result); inclusion of a general footnote under each subtable that 1) all graded values representing a change from baseline must be reported as AEs, with Grade 0 recorded on the AE CRF to indicate grading criteria do not apply and 2) (under each clinical laboratory subtable only) the criteria have been modified for this study based on reference values; and administrative changes to update the list of abbreviations under each subtable and to

Location[a]	Old Text	New Text	Rationale
	(No footnotes) Serum Subtable Serum* Blood urea nitrogen mg/dL 21 – 26 27 – 31 >31 Requires dialysis Creatinine mg/dL 1.5 – 1.7 1.8 – 2.0 2.1 – 2.5 >2.5 or requires dialysis Creatine phosphokinase – mg/dL 2.0 – 5.0 x ***ULN 5.1 – 10.0 x ***ULN 10.1 – 20 x ***ULN >20 x ULN Liver function tests – ALT, AST increase by factor 1.1 – 2.5 x ULN 2.6 – 5.0 x ULN 5.1 x 10 x ULN >10 x ULN Cholesterol 201 – 210 211 – 225 >226 -- Pancreatic enzymes – amylase, and lipase 1.5 – 2.0 x ULN 2.1 – 3.0 x ULN 3.1 – 5.0 x ULN >5.0 x ULN AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase * The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal references should be provided to demonstrate that they are appropriate.	AE = adverse event; CRF = case report form All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0 = absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply. Serum Subtable Serum Blood urea nitrogen increase mg/dL 21 – 26 27 – 31 >31 Requires dialysis Creatinine increase mg/dL 1.5 – 1.7 1.8 – 2.0 2.1 – 2.5 >2.5 or requires dialysis Creatine phosphokinase – increase by factor 2.0 – 5.0 x ULN 5.1 – 10.0 x ULN 10.1 – 20 x ULN >20 x ULN Liver function tests – ALT, AST increase by factor 1.1 – 2.5 x ULN 2.6 – 5.0 x ULN 5.1 – 10 x ULN >10 x ULN Cholesterol increase mg/dL 201 – 210 211 – 225 >226 -- Pancreatic enzymes – amylase, and lipase – increase by factor 1.5 – 2.0 x ULN 2.1 – 3.0 x ULN 3.1 – 5.0 x ULN >5.0 x ULN AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRF = case report form; ECG = electrocardiogram; ULN = upper limit of normal Criteria are modified for this study based on reference values. All graded values representing a change from baseline	remove footnote markers/footnotes that were no longer applicable.

Location[a]	Old Text	New Text	Rationale
		must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0 = absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.	
	Hematology Subtable Hematology* Hemoglobin (Female) - gm/dL 10.5-11.5 9.5-10.4 8.0 – 9.4 < 8.0 Hemoglobin (Male) - gm/dL 12.5 – 13.5 10.5 – 12.4 8.5 – 10.4 < 8.5 WBC Increase - cell/mm^3 10,901 –15,000 15,001 – 20,000 20,001 – 25, 000 > 25,000 WBC Decrease - cell/mm^3 2,500 – 3,500 1,500 – 2,499 1,000 – 1,499 < 1,000 Lymphocytes Decrease - cell/mm^3 750 – 1,000 500 – 749 250 – 499 < 250 Neutrophils Decrease – cell/mm^3 1500-2000 1000-1,499 500-999 < 500 Eosinophils - cell/mm^3 650 – 1500 1501 – 5000 > 5000 Hypereosinophilic PLT - /mm^3 75,000 – 99,000 50,000 – 74,999 20,000 – 49,999 <20,000 PT – increase by factor 1.0 – 1.10 x ULN** 1.11 – 1.20 x ULN 1.21 – 1.25 x ULN > 1.25 ULN Fibrinogen decrease - mg/dL 150 – 200 125 – 149 100 – 124 < 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC) ***ULN is the upper limit of the normal range.	Hematology Subtable Hematology Hemoglobin (Female) decrease - gm/dL 10.5-11.5 9.5-10.4 8.0 – 9.4 < 8.0 Hemoglobin (Male) decrease - gm/dL 12.5 – 13.5 10.5 – 12.4 8.5 – 10.4 < 8.5 WBC increase - cell/mm^3 10,901 –15,000 15,001 – 20,000 20,001 – 25, 000 > 25,000 WBC decrease - cell/mm^3 2,500 – 3,500 1,500 – 2,499 1,000 – 1,499 < 1,000 Lymphocytes decrease - cell/mm^3 750 – 1,000 500 – 749 250 – 499 < 250 Neutrophils decrease – cell/mm^3 1500-2000 1000-1,499 500-999 < 500 Eosinophils increase - cell/mm^3 650 – 1500 1501 – 5000 > 5000 Hypereosinophilic PLT decrease - /mm^3 75,000 – 99,000 50,000 – 74,999 20,000 – 49,999 <20,000 PT – increase by factor 1.0 – 1.10 x ULN 1.11 – 1.20 x ULN 1.21 – 1.25 x ULN > 1.25 ULN Fibrinogen decrease - mg/dL 150 – 200 125 – 149 100 – 124 < 100 or associated with gross bleeding or disseminated intravascular coagulation	

Location[a]	Old Text	New Text	Rationale
	*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. **ULN is the upper limit of the normal range. <u>Urine Subtable</u> Urine* *The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.	PLT = platelet; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal; WBC = white blood cell count Criteria are modified for this study based on reference values. All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0= absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply. <u>Urine Subtable</u> Urine AE = adverse event; CRF = case report form; hpf = high power field; RBC = red blood cell Criteria are modified for this study based on reference values. All graded values representing a change from baseline must be reported as AEs. For clinical or laboratory observations not addressed by the toxicity grading criteria, Grade 0 = absent will be used in the AE CRF to indicate the toxicity grading criteria do not apply.	
Appendix D (now Appendix IV): Schedule of Events (p. 99-102)	Select rows and columns represented as shown ([X] = assessment to be performed; [ ] = assessment not to be performed): Serum pregnancy test[e] Day -21 to -2 [ ] Day -1 [X] Day 15 ± 1 [X] Urine pregnancy test[e] Day -21 to -2 [X]	Select rows and columns represented as shown ([X] = assessment to be performed; [ ] = assessment not to be performed): Serum pregnancy test[e] Day -21 to -2 [X] Day -1 [X] Day 15 ± 1 [X] Urine pregnancy test[e] Day -21 to -2 [X]	Serum pregnancy test added to the screening visit and urine pregnancy test added to Day -1; removal of quantitative platelet function testing; and correction of collection times for stool volume/frequency and

Location[a]	Old Text	New Text	Rationale
	Day -1 [ ] Platelet function test[g] Day -1 [X] Day 1 [X] Day 2 [X] Day 3 [X] Day 4 [X] Day 5 [X] Day 6 [X] Day 7 [X] Day 8 [X[h]] Day 10 ± 1 [X] Day 15 ± 1 [X] Collection of Stool Day -21 to -2 [X] Day -1 [X] Day 1 [X] Day 2 [X] Day 3 [X] Day 4 [X] Day 5 [X] Day 6 [X] Day 7 [X] Day 8 [X] Fecal occult blood assessment Day -21 to -2 [ ] Day -1 [X] Day 1 [X][i] Day 2 [X] Day 3 [X]	Day -1 [X] Stool volume and frequency Day -21 to -2 [ ] Day -1 [ ] Day 1 [X] Day 2 [X] Day 3 [X] Day 4 [X] Day 5 [X] Day 6 [X] Day 7 [X] Day 8 [X] Fecal occult blood assessment Day -21 to -2 [X] Day -1 [ ] Day 1 [X][h] Day 2 [X] Day 3 [X]	fecal occult blood assessment

Location[a]	Old Text	New Text	Rationale
	Day 4 [X] Day 5 [X] Day 6 [X] Day 7 [X] Day 8 [X] Day 15 ± 1 [X][i] Select table footnotes: [g] A subset of hematology (PLT count), serum chemistry (AST, ALT), and coagulation (INR, PT, aPTT) assessments will be collected prior to the first dose only. A quantitative platelet function test with PFA100 will also be assessed prior to the first dose. [h] A quantitative platelet function test with PFA100 will be assessed on day of discharge [i] Fecal occult assessments will be performed prior to the first dose and on Day 8. Fecal occult assessment may be performed as per discretion of the PI.	Day 4 [X] Day 5 [X] Day 6 [X] Day 7 [X] Day 8 [X] Day 15 ± 1 [X][h] Select table footnotes: [g] A subset of hematology (PLT count), serum chemistry (AST, ALT), and coagulation (INR, PT, aPTT) assessments will be collected prior to the first dose only. Note: Footnote [h] deleted and remaining footnotes/footnote markers were renumbered. [h] Fecal occult assessments will be performed on Day 1 starting approximately 6 hours post first dose on every stool sample. On Day 15, fecal occult assessment may be performed as per discretion of the PI, and, if positive, followed until resolution.	

[a]Pagination reflects content placement of the "Old Text" in Protocol Amendment 1, version 2, dated 29 March 2016.

PROTOCOL AMENDMENT 1

Background:

The protocol is being amended in response to the Partial Clinical Hold letter received from the FDA. There are also administrative changes within the protocol which do not affect the safety of subjects, the scope of the investigation, or the scientific quality of the study.

Modifications to the Protocol:

General Revisions:

- Updated the sponsor name and address to Emergent throughout.
- Added sponsor names to sections as appropriate.
- Product Storage and Stability section reorganized.
- Occult blood for all vomitus added throughout as appropriate.
- Fixed typographical errors.

Sectional Revisions:

Table 7: Detailed Changes to Protocol Sections

Location	Old Text	New Text	Rationale
Protocol Summary (Description of Product)	UV-4B (hydrochloride [HCl]) salt of UV-4) oral solution, Appropriate volume of the solubilized drug substance solution in water will be transferred into an oral dosing cup. Ten mL of taste masking agent will be added, and the total volume made up to 30 mL with potable water.	UV-4B (hydrochloride [HCl]) salt of UV-4) oral solution, 30 mg to 150 mg of free base, 30mL including 10mL OraSweet SF taste masking solution. UV-4B clinical trial material is drug substance packaged in double polypropylene bags in HDPE containers and stored at 2-8°C. At time of use, bulk drug substance will be solubilized in water. UV-4B stock solution will be transferred into an oral dosing container, 10 mL of taste-masking agent added, and volume adjusted to 30 mL.	Text edited to clarify product description
Protocol Summary (Description of Placebo)	Taste masking agent, OraSweet-SF, (10 mL) diluted with potable water (20 mL)	Placebo oral solution (10mL OraSweet SF diluted with water)	Text edited to clarify placebo description
Protocol Summary (Secondary Objective)	**Secondary:** To determine pharmacokinetic parameters describing absorption and elimination of UV-4B given TID for 7 days in healthy subjects.	**Secondary:** To determine pharmacokinetic parameters describing absorption and clearance of UV-4B given TID for 7 days in healthy subjects.	Text edited to clarify PK clearance
Protocol Summary (Description of Study Design, paragraphs 2-4)	There is one planned SMC review of all safety and tolerability data and a protocol amendment after completion of the third cohort. The Safety Monitoring Committee (SMC) will also be consulted for any specific safety signals at any point during the study, to include dose-related trends within the normal range. All safety and exposure data from Cohorts 1 through 3 along with a protocol amendment for further dose escalations (Cohorts 4 and 5), if appropriate, will be submitted to the Food and Drug Administration (FDA) for review. In accordance with DMID stated policy, Unither	A Safety Monitoring Committee (SMC) review of all safety and tolerability data will be conducted after completion of each cohort. The SMC will also be consulted for any specific safety signals at any point during the study, to include dose-related trends within the normal range. As requested by the Food and Drug Administration (FDA), safety and pharmacokinetic (PK) data will be submitted for FDA review upon completion of each cohort (1 through 3). The study will be paused during FDA review and dose escalation will only proceed upon approval by the FDA. A protocol amendment for further dose escalations (Cohorts	Text edited to add SMC and FDA review of safety and PK data at the completion of each cohort

Location	Old Text	New Text	Rationale
	will allow for a 30-day FDA review of any such protocol amendment.	4 and 5), if appropriate, will be submitted to DMID, the SMC and the FDA for review after Cohort 3. In accordance with DMID stated policy, Emergent Product Development Gaithersburg, Inc. (Emergent) will allow for a 30-day FDA review of any such protocol amendment.	
Protocol Summary (Description of Study Design, paragraph 5)	Safety assessments will include telemetry, 12-lead electrocardiogram (ECG) measurements, vital signs, physical examinations, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, and fecal occult blood), and adverse events (AEs). Blood samples will be collected for pharmacokinetics at multiple time points until discharge. Plasma will be tested to determine the following parameters for UV-4B in subjects: UV-4 plasma concentrations and pharmacokinetic (PK) parameters determined on day 1 (after first dose up to second dose) and after last dose on Day 7 Maximum plasma concentration [C_{max}] Time to reach maximum plasma concentration [t_{max}] Area under the plasma concentration curve from time zero extrapolated to last quantifiable concentration [$AUC_{(0\text{-}last)}$] (after first dose report $AUC_{(0\text{-}8)}$), Total daily exposure ($AUC_{(0\text{-}24)}$) AUC from time zero extrapolated to infinity [$AUC_{(0\text{-}inf)}$] (Day 7 only), Systemic clearance [CL/F] Volume of distribution [V_z/F], Terminal half-life [$t_{1/2}$] (after last dose),	Safety assessments will include telemetry, 12-lead electrocardiogram (ECG) measurements, vital signs, physical examinations, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, vomitus occult blood and fecal occult blood), and adverse events (AEs). Blood samples will be collected for pharmacokinetics at multiple time points until discharge. Plasma will be tested to determine the following parameters for UV-4B in subjects: UV-4 plasma concentrations and pharmacokinetic (PK) parameters determined on day 1 (after first dose up to second dose) and after last dose on Day 7 Maximum plasma concentration [C_{max}] Time to reach maximum plasma concentration [t_{max}] Area under the plasma concentration curve from time zero extrapolated to last quantifiable concentration [$AUC_{(0\text{-}last)}$] (after first dose report $AUC_{(0\text{-}8)}$), Total daily exposure ($AUC_{(0\text{-}24)}$) AUC from time zero extrapolated to infinity [$AUC_{(0\text{-}inf)}$] (Day 7 only), Systemic clearance [CL/F] Volume of distribution [V_z/F], Terminal half-life [$t_{1/2}$] (after last dose), Accumulation ratio as defined by AUC_(0-8) after the last	Text edited to clarify PK parameters and to add vomitus occult blood per FDA request.

<table>
<tr><th>Location</th><th>Old Text</th><th>New Text</th><th>Rationale</th></tr>
<tr><td></td><td></td><td>dose divided by AUC_(0-8) after the first dose,
The results of these preliminary safety and PK results will be listed and summarized to assist in future dose calculations.</td><td></td></tr>
<tr><td>Protocol Summary (Description of Study Design, paragraph 5)</td><td>Appropriate measures of accumulation,
Time to reach steady state (observed or calculated),
$C_{ss(trough)}$ (trough concentration at steady state, observed or calculated)
The results of these preliminary safety and PK results will be listed and summarized to assist in future dose calculations.</td><td></td><td>Text edited to clarify PK parameters and to add vomitus occult blood per FDA request.</td></tr>
<tr><td>Table 2</td><td>
<table>
<tr><th>Cohort</th><th>Proposed Dose Escalation Scheme</th><th>Dose (mg) TID</th></tr>
<tr><td>1</td><td>Starting dose</td><td>30</td></tr>
<tr><td>2</td><td>Increase 2.5x</td><td>75</td></tr>
<tr><td>3</td><td>Increase 2x</td><td>150</td></tr>
<tr><td colspan="3">FDA and SMC review of all Safety and Tolerability Data and Protocol Amendment</td></tr>
<tr><td>4</td><td>Dose escalation to be determined based on safety data</td><td>TBD</td></tr>
<tr><td>5</td><td>Dose escalation to be determined based on safety data</td><td>TBD</td></tr>
</table>
</td><td>
<table>
<tr><th>Cohort</th><th>Proposed Dose Escalation Scheme</th><th>Dose (mg) TID</th></tr>
<tr><td>1</td><td>Starting dose</td><td>30</td></tr>
<tr><td colspan="3">SMC and FDA review of Safety and PK Data</td></tr>
<tr><td>2</td><td>Increase 2.5x</td><td>75</td></tr>
<tr><td colspan="3">SMC and FDA review of Safety and PK Data</td></tr>
<tr><td>3</td><td>Increase 2x</td><td>150</td></tr>
<tr><td colspan="3">SMC and FDA review of all Safety and PK Data and Protocol Amendment</td></tr>
<tr><td>4</td><td>TBD</td><td>TBD</td></tr>
<tr><td>5</td><td>TBD</td><td>TBD</td></tr>
</table>
</td><td>Added FDA and SMC review of data after each cohort</td></tr>
<tr><td>3.2.1 and 3.2.1 Study Outcome Measures</td><td>3.2.1 Primary Outcome Measures
•Evaluation and occurrence of AEs and serious adverse events (SAEs)</td><td>3.2.1 Primary Outcome Measures
•Evaluation and occurrence of AEs and serious adverse events (SAEs)</td><td>PE, viatal signs and ECG’s moved to secondary outcomes. Clarity</td></tr>
</table>

Location	Old Text	New Text	Rationale
	Determination of changes from baseline for PE, vital signs, ECGs, and clinical laboratory tests **3.2.2 Secondary Outcome Measures** •UV-4 plasma concentrations and PK parameters [including Cmax, tmax, AUC(0-last), AUC(0-8) AUC(0 24), AUC(0 inf), CL/F, Vz/F, t1/2, A_e, f_e, CL_r and appropriate measures of accumulation]	Determination of changes from baseline clinical laboratory tests **3.2.2 Secondary Outcome Measures** •Determination of changes from baseline for PE, vital signs, and ECGs •UV-4 plasma concentrations and PK parameters [including Cmax, tmax, AUC(0-last), AUC(0-8) AUC(0 24), AUC(0 inf), CL/F, Vz/F, t1/2, Ae, fe, CLr and accumulation ratio as defined by AUC_(0-8) after the last dose divided by AUC_(0-8) after the first dose]	added for PK parameters
4.0 Study Design	This is a MAD study with up to five cohorts of healthy subjects planned. Each cohort will consist of 8 subjects (6 active; 2 placebo). Within each cohort, subjects will be randomized to receive UV-4B oral solution or placebo TID for 7 days (every 8 hours ± 0.5 hours). If specific safety criteria are met, then subjects may be enrolled into the next higher dose cohort Safety assessments will include telemetry, 12-lead ECG measurements, vital signs, physical examinations, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, and fecal occult blood), and AEs. Subjects will return to the clinic on Day 10 (±1) for additional safety assessments and blood draws for laboratory assessments and on Day 15 (±1) for the final study follow-up visit. All safety and data from Cohorts 1 through 3 along with a protocol amendment for further dose escalations (Cohorts 4 and 5) if appropriate, will be submitted to the Food and Drug Administration (FDA) and the SMC for review. In accordance with DMID stated policy, Unither will allow for a 30-day FDA review of the protocol amendment.	This is a MAD study with up to five cohorts of healthy subjects planned (18-45 years inclusive) (Table 2). Each cohort will consist of 8 subjects (6 active; 2 placebo). Within each cohort, subjects will be randomized to receive UV-4B oral solution or placebo TID for 7 days (every 8 hours ± 0.5 hours). The study product and placebo will be masked so that the subjects and the site personnel including the PI will be blinded to the treatment assignment. If specific safety criteria are met, then an additional 8 new subjects may be enrolled into the next higher dose cohort Safety assessments will include telemetry, 12-lead ECG measurements, vital signs, physical examinations, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, vomitus occult blood and fecal occult blood), and AEs. Subjects will return to the clinic on Day 10 (±1) for additional safety assessments and blood draws for laboratory assessments and on Day 15 (±1) for the final study follow-up visit. Safety and PK data will be submitted to the SMC and FDA for review upon completion of each cohort. The study will be paused during review. Upon FDA approval, the next	Text edited to add SMC and FDA review after each cohort, to clarify who is blinded to treatment assignment

Location	Old Text	New Text	Rationale
		cohort will be dosed according to the dose escalation outlined in Table 2, unless otherwise modified by the FDA. Upon completion of dosing in the third cohort, safety and PK data and a draft protocol amendment (Cohorts 4 and 5) will be submitted for SMC review. In addition, the cumulative safety and PK summary, minutes and recommendations from the SMC meeting, and the SMC reviewed protocol amendment for Cohorts 4 and 5 will be submitted to the FDA for review. In accordance with DMID stated policy, Emergent will allow for a 30-day FDA review of the protocol amendment.	
5.3.1 Randomization Procedures (second paragraph)	Randomization numbers will be assigned to subjects sequentially using appropriate blocking, following review of all eligibility criteria prior to initiation of any study product administration, and will start with 1001. Table 4 indicates the planned randomization numbers for this study.	Following review of all eligibility criteria, randomization numbers will be assigned to subjects sequentially immediately when subject is dosed. Subjects who are not exposed to study product will not be considered randomized. There may be two back-up subjects per cohort in the event of subject withdrawal prior to dosing. Table 4 indicates the planned randomization numbers for this study.	Text edited to clarify randomization process and back up subjects
5.3.2 Masking Procedures	Masking will be carried out by use of a commercial, sugar-free taste-masking agent (commercially obtained OraSweet-SF). The weight of UV-4B to be solubilized will be determined based on the number of subjects in that cohort and the planned dose as per Table 2**.** An additional intermediate dilution may be included for the lower dose cohorts. Appropriate volume of either water (placebo) or the solubilized drug substance solution will be transferred into an oral dosing cup. Ten mL of the masking agent will be added, and the total volume made up to 30 mL with potable water.	Masking will be carried out by use of a commercial, sugar-free taste-masking agent (commercially obtained OraSweet-SF). This ensures the active and placebo dose solutions match in appearance, taste, and consistency. The weight of UV-4B to be solubilized in the initial stock solution will be determined based on the number of subjects in that cohort and the planned dose as per Table 2**.** An additional intermediate dilution may be included if preferred by the site pharmacy for ease of making solutions. Appropriate volume of either water (placebo) or the solubilized drug substance solution will be transferred into an oral dosing container. Ten mL of the masking agent will be added, and	Text edited to clarify masking procedures

Location	Old Text	New Text	Rationale
		the total volume made up to 30 mL with WFI.	
5.3.3 Reasons for Withdrawal	In all cases of withdrawal, the reason for withdrawal will be recorded. Subjects who are withdrawn from the study will be asked to complete safety assessments including follow-up of any AEs prior to termination from the study. Subjects who are withdrawn from the study will leave the unit after completion of all safety assessments. Subjects withdrawn for reasons other than AEs, after successful inclusion in the study (randomization), will be replaced as appropriate. Up to two subjects per cohort may be replaced at any time during the study.	In all cases of withdrawal, the reason for withdrawal will be recorded. Subjects who are withdrawn from the study will be asked to complete safety assessments for the dose which was completed including follow-up of any AEs prior to termination from the study. Once randomized, subjects who withdraw from the study for any reason will not be replaced.	Text edited to clarify safety assessments for withdrawal from study.
6.1.2 Formulation, Packaging, and Labeling	**UV-4B** For the study, containers of UV-4B will be shipped and stored under 2-8°C refrigerated conditions under locked and limited access. Stability studies of UV-4B batches have indicated that there are increases in water content at the International Conference on Harmonization (ICH) accelerated stability storage condition. Storage at refrigerated conditions limits potential moisture uptake. Aside from moisture uptake, there are no other significant and consistent trends in the stability data reported to date (36 months at 2-8°C condition, 36 months at 25°C/60% relative humidity condition, and 6 months at 40°C/75% relative humidity condition). **Sterile Water for Injection (WFI)** WFI vials are to be stored according to manufacturer specifications at 20-25°C (68°F to 77ºF) [See USP Controlled Room Temperature; excursions between 15°C and 30°C (59°C and 86°F) are permitted].	**6.1.2.1 UV-4B** UV-4B for solubilization for the Phase 1b clinical program is manufactured, packaged, labeled, and released by [redacted] Clinical trial material is UV-4B drug substance, packaged in double bags in containers in a configuration supported by previous and ongoing UV-4B stability programs. [redacted]	Section edited to describe Investigational Product, WFI and Masking agent

Location	Old Text	New Text	Rationale
	OraSweet-SF OraSweet-SF will be stored according to manufacturer specifications.	[redacted] **6.1.2.2 Sterile Water for Irrigation (WFI)** Sterile Water for Irrigation, USP is a sterile, distilled, nonpyrogenic water for injection intended only for sterile irrigation, washing, rinsing, and dilution purposes. It contains no bacteriostat, antimicrobial agent or added buffer and is supplied only in single-dose containers. WFI will be used to solubilize the UV-4B drug substance, for intermediate UV-4B dilutions, and for placebo preparation. **6.1.2.3 OraSweet-SF** Commercially available OraSweet-SF contains purified water, glycerin, sorbitol, sodium saccharin, xanthum gum, and flavoring. It is buffered with citric acid and sodium citrate and contains methylparaben, potassium sorbate, and propylparaben as preservatives. OraSweet-SF will be used as a taste-masking agent and for the placebo preparation. Use of OraSweet SF ensures the active and placebo dose solutions match in appearance, taste, and consistency. Masking procedures are described in 5.3.2.	
6.1.3.2 Sterile Water for ~~Injection~~ Irrigation (WFI)	WFI vials are to be stored according to manufacturer specifications at 20-25°C (68°F to 77ºF) [See USP Controlled Room Temperature; excursions between 15°C and 30°C (59°C and 86°F) are permitted].	Store according to manufacturer specifications at 20-25°C (68°F to 77ºF) [See USP Controlled Room Temperature; excursions between 15°C and 30°C (59°C and 86°F) are permitted]. Protect from freezing.	Text edited to update information per package insert.
9.2.2 Serious Adverse Events (bulleted list)	**All SAEs will be :** • Recorded on the appropriate eCRF; • Followed through to resolution by a study clinician; • Reviewed and evaluated by a study clinician.	**All SAEs will be :** • Recorded on the appropriate eCRF; • Followed through to resolution by a study PI; • Reviewed and evaluated by a study PI.	Text edited to further define what would happen if an SAE occurs during the study.

Location	Old Text	New Text	Rationale
		• Recorded on the SAE Data Form and forwarded within 24 hours by fax or email to Emergent Pharmacovigilance. • Sent to DMID Medical Monitor	
9.3.2 Reporting of Pregnancy (first paragraph)	A pregnancy reporting form will be completed for any female study subject or for any female partner of a male study subject who becomes pregnant following their exposure to study product (Day 1) through 3 months after the last dose of study product. All pregnancies will also be reported as a protocol deviation. The site will maintain contact through at least monthly telephone calls with pregnant study subjects to obtain pregnancy outcome information. The pregnant subject will be followed by monthly telephone calls until 2 months after the birth of the baby or until the end of the pregnancy (in case pregnancy is terminated). Infants born to these study subjects will also be monitored for SAEs for up to 2 months after birth (information regarding SAEs will be captured on the pregnancy reporting form and the SAE form). Pregnancy reporting forms will be limited to collecting data on the following information:	A Notification of Pregnancy form will be completed for any female study subject or for any female partner of a male study subject who becomes pregnant following their exposure to study product (Day 1) through 3 months after the last dose of study product and forwarded within 24 hours of awareness by fax or e-mail to Emergent Pharmacovigilance. All pregnancies will also be reported as a protocol deviation. The site will maintain contact through at least monthly telephone calls with pregnant study subjects to obtain pregnancy outcome information. The pregnant subject will be followed by monthly telephone calls until 2 months after the birth of the baby or until the end of the pregnancy (in case pregnancy is terminated) which time the Pregnancy Outcome form will be completed and forwarded to Emergent Pharmacovigilance. Infants born to these study subjects will also be monitored for SAEs for up to 2 months after birth (information regarding SAEs will be captured on the Pregnancy Outcome form and the SAE form). Pregnancy Outcome forms will be limited to collecting data on the following information :	Text edited to clarify pregnancy outcome reporting
9.5 Dose Escalation	The study will proceed to the next planned dose level when it is confirmed that **NONE** of the following criteria were met and the PI, UV Medical Monitor and ISM are notified: 2 or more of the subjects in the cohort experience an AE, graded 2 or above in the same organ class attributed to	The SMC will review of all safety and PK data after completion of each cohort. Upon completion of review by the SMC, safety summary and PK data will be sent to the FDA for review and approval to continue with dose escalation.	Text deleted because dose escalation will be determined by the FDA

Location	Old Text	New Text	Rationale
	study product (e.g. 2 or more subjects experience a 4 fold increase from ULN for AST and/or ALT) Any subject experiences a single AE graded 3 or above attributed to study drug If any of the above criteria are met, escalation to the next planned dose will not proceed until all currently available study data have been reviewed by the SMC, if the SMC recommends to escalate at a lower dose than planned, a protocol amendment will be done. If subjects terminate study participation early, to ensure adequate PK and safety data in the given cohort, up to 4 subjects may be replaced after agreement between the PI and the UV medical monitor. Additionally, the following criteria must be met: Minimum of 7 subjects complete the cohort Subject data through Day (15±1)		
9.6 Study Halting Criteria	An SAE that results in anaphylaxis (type I HS), or other hypersensitivity reactions (i.e. histamine mediated reactions), or death An SAE that is determined to be either drug-related or of unknown causality; Three or more subjects within a cohort, with the same Grade 2 event attributed to study product ; Any single Grade 3 or above finding attributed to study product (with the exception of aPTT as explained below); Any other findings that, at the discretion of the PI, indicate that the study should be halted;	Any SAE Three or more subjects within a cohort, with the same Grade 2 event ; Any single Grade 3 or above finding (with the exception of aPTT as explained below); Evidence of hematemesis or hematochezia in 2 or more subjects Any other findings that, at the discretion of the PI, indicate that the study should be halted;	Text edited to reconcile criteria with FDA recommendations
9.7 Individual Dose	Any single grade 3 AE or Lab abnormality (unless determined to be unrelated to IP)	Any single grade 3 AE or Lab abnormality Fecal occult blood remains positive for 3 days, hemorrhoids	Text edited to reconcile criteria

Location	Old Text	New Text	Rationale
Limiting Toxicity	Fecal occult blood remains positive for 3 days, hemorrhoids are excluded Any clinical signs or symptoms the PI has determined is unsafe to administer IP	are excluded Evidence of frank hematemesis or hematochezia/melena of any duration Any clinical signs or symptoms the PI has determined is unsafe to administer IP	with FDA recommendations
11.2 Sample Size Considerations	The sample size chosen for this study is not based on statistical considerations. The number of subjects within each dose group was chosen based on historical experience with safety and tolerance trials. The sample size falls within the range of those used in other studies of this nature.	The study will enroll 8 subjects in each cohort for up to 5 cohorts. In each cohort, 6 subjects will be randomized to receive UV-4B and 2 will receive placebo The number of subjects within each dose group was chosen based on historical experience with safety trials. Based on the site's experience with similar MAD studies, early discontinuation rate is typically 10-15%, and withdrawals generally occur after subjects are discharged from the clinic. As the collection of PK data will occur during the 7-day in-clinic dosing period, this will allow a sufficient number of subjects for adequate characterization of the PK profile. All subjects, even those discontinuing early, will be included in the safety analysis, and subject follow up will occur as per protocol to determine any safety-related events. Therefore, no subjects who terminate study participation early will be replaced.	Text edited to add rationale for sample size considerations
11.3 Planned Interim Analyses	Initiation of dosing in subsequent cohorts will occur only after assessment of safety and plasma PK parameters from the previous cohort have been completed.	After completion of the third cohort, a summary report will be provided to the SMC, including tables and listings of all data for each cohort. Summary safety and PK data will also be provided to the FDA after the completion of each cohort. All data will remain blinded.Initiation of dosing in subsequent cohorts will occur only after assessment of safety and plasma PK parameters from the previous cohort have been completed.	Text edited to clearly define analysis after Cohort 3

Location	Old Text	New Text	Rationale
11.4.4 Statistical Plan	A formal statistical analysis plan for the analysis and presentation of data from this study will be prepared before database lock. In the event of loss of subjects during cohort enrollment, additional study subject(s) which meet all screening criteria may be added. Statistical instruments used to allow for study continuance and subject replacement include use of Linear mixed effects model and multiple imputation algorithms.	A formal statistical analysis plan for the analysis and presentation of data from this study will be finalized before database lock.	Text edited to clarify finalization of the SAP
11.4.5 Safety (first paragraph)	There are no statistical rules for stopping the study; however, halting rules are given in Section 9.6. After completion of the third cohort, a summary report will be provided to the SMC, including tables and listings of AEs for each cohort. Safety summary and PK data will also be provided to the FDA after the completion of the third cohort. All data will remain blinded.	None	Text deleted and information was added to section 11.4.4
11.4.6 Pharmacokinetics	Pharmacokinetic parameters will be calculated by noncompartmental techniques using WinNonlin Professional® Version 5.2 or higher. All calculations for final plasma parameter analysis will be based on nominal sampling times. Interim PK analysis will be based on scheduled sampling times. The following single dose plasma parameters will be estimated from the plasma concentration-time data, as appropriate: C_{max} t_{max} $AUC_{(0\text{-}last)}$ $AUC_{(0\text{-}8)}$ ($AUC_{(0\text{-}24)}$	Pharmacokinetic parameters will be calculated by noncompartmental analysis using WinNonlin Professional® Version 5.2 or higher. All calculations for final plasma parameter analysis will be based on nominal sampling times. PK analysis will be performed at the completion of each cohort. The following PK parameters will be estimated: C_{max} t_{max} $AUC_{(0\text{-}last)}$ $AUC_{(0\text{-}8)}$ ($AUC_{(0\text{-}24)}$ $AUC_{(0\text{-}inf)}$	Text edited to clarify PK parameters and analysis process.

Location	Old Text	New Text	Rationale
	$AUC_{(0\text{-}inf)}$ λz CL/F $Vz/Ft_{1/2}$ Appropriate measures of accumulation Additional UV-4 PK parameters may be calculated at the discretion of the pharmacokineticist. Plasma concentrations and plasma PK parameters will be summarized by treatment using descriptive statistics, as appropriate. Figures for the arithmetic mean (and SD) concentration-time data will be presented for all doses on both a linear and semi-logarithmic scale. Individual concentration-time data will be graphically presented on linear and semi-logarithmic scales. Scatter plots of individual and geometric mean PK parameters versus dose will be presented. Additional graphical presentations of PK data may be added at the discretion of the PK analyst. Dose proportionality of C_{max}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$ will be assessed graphically and statistically using the power model approach with the logarithm of PK parameters $AUC_{(0\text{-}inf)}$ and C_{max} as the dependent variables and the logarithm of the dose as the independent variable: ($[AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}last)}$, or $C_{max}]=\alpha*dose^{\beta}$). Appropriate measures of accumulation will be reported.	CL/F Vz/F $t_{1/2}$ Accumulation ratio as defined by AUC_(0-8) after the last dose divided by AUC_(0-8) after the first dose Plasma concentrations and plasma PK parameters will be summarized by cohort. PK parameters will also be presented in graphs as detailed in the SAP. Dose proportionality of C_{max}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$ will be assessed graphically and statistically using the power model approach with the logarithm of PK parameters $AUC_{(0\text{-}inf)}$ and C_{max} as the dependent variables and the logarithm of the dose as the independent variable: ($[AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}last)}$, or $C_{max}]=\alpha*dose^{\beta}$).	