CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 15-0108
Study Title:
A Phase 1, Double-blinded, Placebo Controlled, Clinical Trial to Evaluate the Safety, Reactogenicity, and Immunogenicity of HEV-239 (Hecolin®) in a Healthy US Adult Population

NCT03827395

Version 1.0

DATE: 2-November-2020

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 15-0108**
Development Phase:	Phase 1
Products:	HEV-239 (Hecolin®)
Form/Route:	Intramuscular injection (IM)
Indication Studied:	Hepatitis E
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	April 12, 2019
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This study was performed in compliance with Good Clinical Practice.

TABLE OF CONTENTS

Table of Contents *(continued)*

Table of Contents *(continued)*

LIST OF ABBREVIATIONS

A/C.O.	Absorbance Value / Cut-Off Value
AEs	Adverse Events/Adverse Experiences
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
BMI	Body mass index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
Cr	Creatinine
CSR	Clinical Study Report
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
FDA	Food and Drug Administration
GMCs	Geometric Mean Concentrations
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HgB	Hemoglobin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IM	Intramuscular
mITT	Modified intent-to-treat
MedDRA®	Medical Dictionary for Regulatory Activities
µg	Micrograms
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIH	National Institutes of Health

List of Abbreviations *(continued)*

ORF	Open reading frames
PBMC	Peripheral Blood Mononuclear Cell
PFS	Pre-filled syringe
PP	Per protocol
PT	Preferred Term
RCD	Reverse cumulative distribution
SAE	Serious Adverse Events/Serious Adverse Experiences
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
US	United States
VLP	Virus Like Particle
VTEU	Vaccine Treatment and Evaluation Unit
WBC	White blood cell count
WFI	Water for Injection
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 1, Double-blinded, Placebo Controlled, Clinical Trial to Evaluate the Safety, Reactogenicity, and Immunogenicity of HEV-239 (Hecolin®) in a Healthy US Adult Population" (DMID Protocol 15-0108) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for immunogenicity and safety outcomes, and (4) a list of proposed tables and figures. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis worldwide causing an estimated 20 million infections, 3.3 million cases of symptomatic disease, and 70,000 deaths annually. [1, 2] The symptoms of acute HEV infection include fever, vomiting, myalgias, and malaise, followed by progression in some to jaundice, acholic stools, darkened urine, and elevated liver transaminases. [3] Adults are more likely to develop symptomatic disease than children, and pregnant women are most severely affected with mortality rates of 10 – 30% in the third trimester. Mother-to-infant transmission may also occur, resulting in fetal loss and increased perinatal morbidity and mortality. [4, 5] Unfortunately, supportive care is the only medical therapy available for hepatitis E. HEV is mainly transmitted via the fecal-oral route due to contaminated water although vertical and iatrogenic transmission from infected blood products can occur. HEV is responsible for sporadic cases and large outbreaks in the developing world and disproportionally affects areas with poor hygiene standards and population crowding such as refugee camps. [6, 7] Although less common, HEV also causes sporadic cases in industrialized nations, and the disease burden may be underestimated. [8]

HEV-239 is a 26kDa protein expressed in Escherichia coli as a non-fusion virus-like particle (VLP). It was licensed in 2012 for use in China and is produced and marketed by Xiamen Innovax Biotech Co. Ltd. HEV-239 encompasses the neutralizing epitope within the (P) domain (amino acid 368-606; 239 amino acids in length). The purified protein is adsorbed to aluminum hydroxide in buffered saline and then packaged into a pre-filled syringe for Intramuscular (IM) use. Approval and licensure in China was based on a Phase III clinical trial of HEV-239 conducted in 112,604 healthy Chinese adults (16-65 years). The study was a randomized, double-blinded, placebo-controlled (1:1 ratio) trial which evaluated the safety, immunogenicity, and efficacy of HEV-239 in subjects from 11 townships in the Jiangsu Province of China from August 2007 to June 2009. [9] Subjects were randomized to receive three doses of either 30 micrograms (µg) HEV-239 or placebo (a licensed hepatitis B vaccine) administered intramuscularly at 0, 1, and 6 months. The primary endpoint was prevention of hepatitis E during the 12 months following the 31st day after the third vaccine dose. Overall, the vaccine was well tolerated with similar systemic adverse events (AEs) but slightly higher rates of swelling and pain in HEV-239 recipients in comparison to placebo. Serious adverse events (SAEs) and deaths were similar between the groups. SAEs within 30 days of any dose (0.4% versus 0.4%), SAEs after the 30 day window periods (2.5% versus 2.5%), and deaths (0.2% versus 0.2%, none were considered related) were similar between vaccine and placebo recipients respectively. SAEs that were reported in the Phase 3 study were considered unrelated to study vaccine by the Data Safety Monitoring Board (DSMB). In subjects who received either 2 or 3 doses of vaccine, 100% protection against pre-specified hepatitis E infection was observed. [9] A follow-up study was subsequently conducted through 4.5 years for evidence of hepatitis E infection. [10] In that study, 7 cases of hepatitis E were identified in vaccine recipients versus 53 in placebo recipients. [10]

A vaccine against HEV that has undergone safety and immunogenicity testing outside of China would be very beneficial. Such a vaccine could provide protection for travelers or be used in outbreaks to prevent continued transmission of disease. It also would be highly beneficial in preventing maternal, fetal, and infant deaths. The vaccine, though licensed in China, is neither FDA approved nor World Health Organization (WHO) prequalified. Although vaccine safety is established in a Chinese population, safety in other population cannot be presumed. Data are needed establishing its safety and immunogenicity in other populations. This Phase I study will use the dose (30 µg), dosing schedule (0, 1, and 6 months), and route of administration (IM) that was used in the Phase 3 study in China.

The purpose of this Phase 1 randomized-controlled double-blind study is to assess the safety, reactogenicity, and immunogenicity of HEV-239 in healthy adults in the U.S. Twenty-five subjects will be randomized (4 vaccine: 1 placebo) to receive vaccine (n = 20) or placebo (n = 5). Each subject will receive 3 injections,

either vaccine or placebo at Days 1, 29, and 180. Subjects will be followed through 12 months for safety and durability of the immune responses observed.

2.1. Purpose of the Analyses

These analyses will assess the safety, reactogenicity, and immunogenicity of HEV-239 administered in three successive intramuscular injections and will be included in the clinical study report.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary

- Assess the safety and reactogenicity of HEV-239 following delivery of each vaccine dose.
- Assess the number of subjects with ≥4-fold rise in HEV Immunoglobulin (Ig) G at any time after vaccination.

3.1.2. Secondary

- Assess the number of subjects with HEV IgM seroconversion at any time after vaccination.
- Assess the number of subjects with HEV IgG seroconversion at any time after vaccination.
- Assess the HEV IgG geometric mean concentrations (GMCs) at any time after vaccination.

3.2. Endpoints

3.2.1. Primary

- Determine the number of solicited local and systemic reactogenicity events from the time of study vaccination through Day 8 after each study vaccination.
- Determine the number of vaccine-related unsolicited adverse events (AE) from the time of each study vaccination through Day 29 after each study vaccination.
- Determine the number of clinical safety laboratory AEs at Day 8 after each study vaccination.
- Determine the number of vaccine-related serious adverse event (SAE) from the time of first study vaccination through 6 months after the last dose of vaccine.
- Determine the number of subjects showing ≥4-fold rise in serum HEV IgG concentration by Enzyme-linked Immunosorbent Assay (ELISA) from the baseline at Days 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360.

3.2.2. Secondary

- Determine the number of subjects with HEV IgM seroconversion by ELISA at Days 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360.
- Determine the number of subjects with HEV IgG seroconversion by ELISA at Days 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360.
- Determine the HEV IgG GMCs by ELISA in subjects at Days 1, 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360.

3.3. Study Definitions and Derived Variables

The baseline value will be defined as the last value obtained prior to the first vaccination/dose of study product.

Seronegative samples will be defined as per the Wantai HEV-IgM and IgG ELISA package inserts (Absorbance Value / Cut-Off Value (A/C.O.) <0.9).

Seroconversion will be defined as a change from a seronegative result to a seropositive result as defined by the Wantai HEV-IgM and IgG ELISA package inserts (A/C.O. >1.1). Samples with borderline A/C.O. values (0.9-1.1) will be retested in duplicate. If both retests are negative (as defined above), the result will be reported as negative. If one or both retests are positive, the result will be reported as positive. If both retest values are in the borderline zone, the result will be reported as indeterminant.

A 4-fold seroconversion will be defined as a HEV IgG ≥0.154 in a subject that was HEV seronegative at baseline.

Duration of solicited events will be defined as the number of contiguous symptomatic days.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a phase 1, single center, randomized, double-blinded, placebo controlled clinical trial in which 25 healthy males and non-pregnant females 18-45 years of age who meet all eligibility criteria receive 3 doses of HEV-239 vaccine or receive 3 doses of placebo, randomized in a 4:1 ratio. Subjects will be screened by medical history, physical exam, and clinical laboratory tests, including a urine or serum pregnancy test for women of childbearing potential. A schematic of the study design is presented in Figure 1.

4.2. Discussion of Study Design, Including the Choice of Control Groups

This study is designed to determine the safety and immunogenicity of HEV-239 administered via intramuscular injection. Five placebo subjects are included in order to reduce observer bias and are not intended to be a comparison group.

4.3. Selection of Study Population

The study population for DMID protocol 15-0108 is males and non-pregnant females, 18 to 45 years old, inclusive, who are in good health and meet all eligibility criteria. Potential subjects will be recruited from the general community surrounding Emory University in Atlanta. Subjects will be screened by medical history, physical exam, and clinical laboratory tests.

4.3.1. Subject Inclusion Criteria

Prospective subjects must meet all of the following inclusion criteria to be considered eligible for enrollment:

1. Subject must provide written informed consent
2. Subject must be able to comprehend and willing to comply with all study visits and procedures (up to 13 months from enrollment).
3. Subject must be a man or a non-pregnant woman[1] aged 18-45 years (inclusive).

   [1]Females of childbearing potential must have a negative serum human chorionic gonadotropin (β-HCG) pregnancy test at screening and negative urine β-HCG pregnancy test within 24 hours prior to (each) vaccination.
4. Subject must be in good general health as determined by medical history, vital signs,[2] body mass index (BMI),[3] physical examination, and clinical judgment of the investigator.

   [2]Oral temp <38.0°C/100.4°F; pulse 51 to 100 bpm; systolic blood pressure 90 to 140 mm Hg, and diastolic blood pressure 55 to 90 mmHg.

   [3]BMI ≥18.5 and <35 kg/m^2.
5. Subject's screening laboratory values[4,5] must be within site normal limits[6] within 28 days of enrollment.

   [4]Screening labs will include:
   - White blood cell (WBC) count

- Hemoglobin (HgB)
- Platelets
- Absolute neutrophil count (ANC)
- Absolute eosinophil count (AEC)
- Creatinine
- Glucose (random, must be <140)
- Alanine Aminotransferase (ALT)
- HIV 1/2 antibody/antigen test, Hepatitis B surface antigen (HBsAg), and Hepatitis C virus (HCV) antibody

[5]Minor abnormalities are considered acceptable if not clinically significant (e.g., MCV). Repeating the screening tests once is permitted for out-of-range values provided there is an alternative explanation for the out-of-range value. The alternative explanation for the out-of-range value should be documented in the subject's source documents.

[6]See Table 6 for site normal values. Creatinine, glucose, and ALT values lower than the normal range may be acceptable if the PI or a designated licensed clinician determines that these laboratory findings are not clinically significant. The HIV 1/2 antibody/antigen test, Hepatitis B surface antigen (HBsAg), and Hepatitis C virus (HCV) antibody must be non-reactive.

6. Subject's HEV-specific IgG and IgM are negative by ELISA at screening.
7. Subject agrees to not to participate in another clinical trial during the study period.
8. Subject agrees not to donate blood from screening through Day 270.
9. Female subjects must be of non-childbearing potential[7] OR must use an acceptable method of contraception[8] from 28 days before prime vaccination until at least 3 months after the last vaccination.

   [7]Surgically sterile via tubal ligation, bilateral oophorectomy, hysterectomy or postmenopausal for ≥1 year.

   [8]Abstinence (defined as refraining from heterosexual intercourse), monogamous relationship with vasectomized partner, barrier methods such as male or female condoms with spermicide or diaphragms with spermicide, intrauterine devices, and licensed hormonal methods (such as birth control pills, skin patches, Implanon®, Nexplanon®, DepoProvera®, or NuvaRing®).

10. Male subjects must be surgically sterile via vasectomy OR must use an acceptable method of contraception[9] from prime vaccination until at least 3 months after the last boost vaccination.

    [9]Abstinence (defined as refraining from heterosexual intercourse), or condoms with spermicide.

11. Subjects must have consistent access to the internet to perform electronic data entry.

4.3.2. Subject Exclusion Criteria

Prospective subjects must not meet any of the following exclusion criteria to be considered eligible for enrollment:

1. Has a previous HEV infection or chronic liver disease.
2. Has received any experimental agent[10] within 30 days prior to first vaccination, or the expected recipient of any experimental agent during this trial-reporting period.

   [10]Including vaccines, drugs, biologics, devices, and/or blood products

3. Female subject is pregnant (or has a positive pregnancy test prior to vaccination) or breast feeding, or planning to become pregnant within 3 months after the last boost vaccination.
4. Fever (≥38.0°C/100.4°F) or other acute illness within 3 days prior to first vaccination.
5. Infection requiring systemic antibiotics or antiviral treatment within the 7 days prior to first vaccination.
6. Has a positive urine drug screen for amphetamines[11], cocaine, opiates, or phencyclidine.

   [11]Prescription amphetamines are not exclusionary.
7. Chronic, clinically significant medical or psychiatric conditions that,[12] in the opinion of the investigator, may pose additional risk to the subject if she/he participates in the study.

   [12]Permissible conditions include but are not limited to mild, well-controlled asthma, well-controlled depression, well-controlled anxiety, seasonal allergies, and well-controlled hypertension.
8. Receipt of immunosuppressive drugs[13-15] or biologic agents within the 30 days prior to enrollment.

   [13]This includes use of oral or parental prednisone. This also includes allergy desensitization injections from 14 days prior to each vaccination through 14 days after each vaccination. The use of topical steroids for mild uncomplicated dermatitis permissible after therapy is completed. Over-the-counter (OTC) corticosteroid nasal sprays for allergic rhinitis are permissible. The use of low or moderate dose inhaled steroids is permissible. Doses are defined as per age as using inhaled high-dose per reference chart in the National Heart, Lung and Blood Institute Guidelines for the Diagnosis and Management of Asthma (EPR-3) or other lists published in UPTODATE.

   [14]Receipt of systemic, prescription medications for the treatment of chronic medical conditions or variations of normal physiologic functions may be permissible if, in the opinion of the investigator, they are used for conditions that are not clinically significant and would not impact the safety of the subject or the safety and immunogenicity outcomes of the protocol.

   [15]Use of systemic, over-the-counter medications and PRN systemic, prescription medication may be allowed if, in the opinion of the investigator, they pose no additional risk to subject safety or assessment of immunogenicity/reactogenicity.
9. Has known neoplastic disease[16] anticancer therapy, or radiation therapy within 3 years prior to first study vaccination.

   [16]Excluding non-melanoma skin cancer, such as squamous cell skin cancer or basal cell skin cancer, cured by surgical excision.
10. Has a history of any hematologic malignancy at any time.
11. Has a known or suspected congenital or acquired disease that impairs the immune system, including functional asplenia or immunosuppression as a result of underlying illness or treatment.
12. Has prior organ and/or stem cell transplant.
13. Has a history of abuse of alcohol or drugs that, in the opinion of the investigator, may interfere with the subject's ability to comply with the protocol.

14. Has behavioral or cognitive impairment or psychiatric conditions that, in the opinion of the investigator, may interfere with the subject's ability to participate in the trial.
15. Has received blood products or immunoglobulin within six months prior to vaccination.
16. Travel to Asia, the Middle East, Africa, or Central America or to an area with an active Hepatitis E outbreak[17] within the last 90 days or intention to travel to such areas during the study.

    [17]See study-specific Manual of Operating Procedures (MOP) for a listing of outbreaks within the last 3 years.
17. Receipt of any inactivated vaccine from 2 weeks prior to each vaccination through 2 weeks after each vaccination.
18. Receipt of any live vaccine from 4 weeks prior to each vaccination through 4 weeks after each vaccination.
19. Known hypersensitivity or allergy to aluminum, any component of the vaccine, or other serious adverse reactions to vaccines or vaccine products.
20. Subject who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study.
21. Any condition that, in the opinion of the investigator, might interfere with assessing the study objectives.

4.4. Treatments

4.4.1. Treatments Administered

Subjects will be administered three doses of either HEV-239 vaccine or placebo.

4.4.2. Identity of Investigational Product(s)

HEV-239 (Hecolin®)

HEV-239 is a recombinant protein vaccine for the prophylaxis of HEV group 1. The Chinese group 1 HEV strain was used to provide the open reading frame 2, which encodes a 239 amino acid long sub-fragment of the HEV capsid protein. The HEV-239 protein is then expressed in E. coli ER2566 transfected with the expression vector pTO-T7 containing the HEV-239 gene. The pTO-T7 prokaryotic vector was derived by inserting the T7 promoter and ribosome binding site of pET11a (New England Biolabs) and a plant-derived enhancer upstream of the promoter (Xiamen University). The recombination procedure has been previously described. [11]

Kanamycin resistant bacterial clones were selected and recombinant plasmid verified by DNA sequencing for the inserted fragment. The HEV-239 protein expressed by this recombinant plasmid assembles into virus like particles (VLP). The purified VLP (vaccine) is mixed with an aluminum adjuvant and packaged as pre-filled syringes (PFS).

Placebo (Sterile Normal Saline)

0.9% Sodium Chloride Injection, USP (Normal Saline) is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection (WFI). This product is used as the placebo and is packaged in single use containers. Each mL contains sodium chloride 9mg and may contain HCl or NaOH for pH adjustment (pH 5.3 [4.5 – 7.0]). It contains no bacteriostatic, antimicrobial agent, preservative or added buffer.

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Enrollment/randomization will be performed through the enrollment module in the electronic data capture system, maintained by the Statistical and Data Coordinating Center (SDCC).

Eligible subjects will be randomized and assigned in a 4:1 ratio to HEV-239:placebo. The randomization is based on a variable blocked scheme to provide an approximately balanced allocation to the treatment groups during the study.

4.4.4. Selection of Doses in the Study

DMID protocol 15-0108 will use the dose (30 μg) and route of administration (IM) which were found to be safe and well-tolerated in the Phase 3 study in China. [9]

4.4.5. Selection and Timing of Dose for Each Subject

Subjects will receive three doses administered intramuscularly in clinic at Day 1, Day 29, and Day 180. This was the dosing schedule used in the Phase 3 study in China. [9]

4.4.6. Blinding

This is a double-blind study. Subjects, investigators, study personnel performing any study-related assessments following study vaccine administration, and laboratory personnel performing antibody assays will be blinded to whether the subject received placebo or HEV-239.

The randomization scheme will be generated by the SDCC and provided to unblinded study personnel including pharmacists performing study vaccination preparations and unblinded study vaccine administrator.

The unblinded study vaccine administrator is a study personnel member credentialed to administer vaccines and may also participate in dose preparation, but will not be involved in study-related assessments or have subject contact for data collection following study vaccine administration. He or she will only be involved with vaccine administration.

The protocol contains no explicit provisions for emergency unblinding. According to DMID policy, the study medical monitor responds to requests for emergency unblinding, and instructs the SDCC to release treatment codes only if necessary to ensure that the subject receives appropriate clinical care.

4.4.7. Prior and Concomitant Therapy

Medications history (concomitant medications) will include a review of all current medications and medications taken within 30 days prior to signing the informed consent form through Day 57, or Day 29 for those who only receive one dose of study vaccine, or early termination (if prior to Day 29 after any study vaccine dose), whichever occurs first. Concomitant medications will also include all current medications and medications taken within 30 days prior to Vaccine Dose 3 (Day 180) through Day 208. Concomitant therapies outside these times will only be recorded if administered in conjunction with SAEs. Prescription and over-the-counter drugs and vaccines will be included as well as vitamins, herbals, and supplements. Prohibited prior

therapies include blood products or immunoglobulin within six months prior to first vaccination and immunosuppressive drugs or biologic agents within the 30 days prior to first vaccination. Prohibited concomitant therapies include inactivated vaccines from 2 weeks prior to each vaccination through 2 weeks after each vaccination and live vaccines from 4 weeks prior to each vaccination through 4 weeks after each vaccination.

4.4.8. Treatment Compliance

All subjects are to receive 3 doses of study product administered in the clinic. Subjects will be directly observed at the time of dosing by a member of the clinical research team who is licensed to administer vaccines. Administration will be documented on the Treatment Administration electronic case report form (eCRF) in Advantage eClinical.

4.5. Immunogenicity and Safety Variables

See Table 1 for a schedule of study procedures.

Multiple observations within a specific visit period are accepted. In the case of multiple observations within a specific window, the assessment value that is closest to the scheduled visit window will be used in the analyses for the post-baseline records. For screening and baseline visits, the last assessment value will be used. All the recorded data will be listed. If observations have the same distance to the scheduled assessment, the latest one will be used.

4.5.1. Safety Variables

Adverse Events (AEs): ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

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

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

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

Adverse Events Grading: All AEs (laboratory and clinical symptoms) will be graded for severity and assessed for relationship to study product (see definitions). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the

appropriate data collection form and eCRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

Severity of Event: AEs will be assessed by the investigator using a protocol-defined grading system (toxicity table included as an appendix). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

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

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

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

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

Reactogenicity (Solicited Local and Systemic Events): Reactogenicity events are AEs that are common and known to occur following administration of this type of study vaccine. The subject will be instructed on noting the presence and severity of symptoms through D8 after administration of study vaccine. Solicited events will be graded per Table 4 and Table 5.

Any symptoms still present at the D8 visit after each vaccination will continue to be followed by subject until symptom resolution. Subjects will also be asked to call the site if they experience any severe symptoms other than what is listed on the e-Memory aid, if they have any severe symptoms that prevents daily activity or any other symptoms and health complaints, even if they are not listed on the e-Memory aid. Sites will review the concomitant medications with the subject at subsequent clinic visits. The subject's input into the electronic data capture system will be reviewed with the subject at subsequent clinic visits.

Subjects will be instructed on how to record daily temperature using a thermometer provided for home use. Subjects should record the oral temperature in the evening post vaccination, and then daily through D8 after each vaccination. Temperature should be measured at approximately the same time each day. If more than one measurement is made on any given day, the highest temperature will be recorded. This information will be reviewed by study staff during follow-up subject contacts.

The site PI/study staff will also assess the vaccination site and measure edema and erythema at the visits post vaccination. Vital sign measurements will be performed at the time points indicated in Section 9.7 . Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest and in a quiet setting without distractions (e.g., television, cell phones). Confirmatory vital sign measurements can be performed if inconsistent with a prior measurement. A symptom-directed examination will be performed as indicated by the investigator based on any clinically relevant issues, clinically relevant symptoms and medical history. The symptom-directed PE may be repeated if deemed necessary by the investigator. PEs will be performed by a study clinician licensed to make medical diagnoses and listed on the FDA Form 1572 as the site principal investigator or sub-investigator.

Serious Adverse Events (SAEs): An AE or suspected adverse reaction is considered a serious adverse event (SAE) if, in the view of either the site principal investigator or sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening adverse event[1],
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

SAEs will be:

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

Safety will be assessed by the frequency and severity of:

1. Serious adverse events occurring from the time of the first study vaccination through the last study visit (Day 360).

2. Solicited Adverse Events – reactogenicity events occurring on the day of each study vaccination through Day 8 after each study vaccination:
   a) Injection site reactions including pruritus (itching), ecchymosis (bruising), erythema (redness), induration (hardness)/swelling, pain, and tenderness.
   b) Systemic reactions including fever, feverishness (chills/shivering/sweating), fatigue (tiredness), malaise (general unwell feeling), myalgia (body aches/muscular pain exclusive of the injection site), arthralgia (joint pain exclusive of the injection site), headache, nausea, and vomiting.
3. Clinical safety laboratory AEs at Day 8 after each study vaccination. Parameters to be evaluated include WBC, ANC, AEC, Hgb, PLT, Cr, and ALT.
4. Unsolicited Adverse Events (see Section 8.1.3) – non-serious adverse events occurring from the time of the first study vaccination until Day 57 and then from Day 180 through Day 208. Unsolicited AEs will be collected at all visits from the time of the first study vaccination until D57, then from Day 180 through 208. Any safety-related changes that occur post-vaccination during these timeframes and that represent an increase in grade must be recorded on the eCRF. Thereafter, recording will be limited to SAEs.

4.5.2. Immunogenicity Variables

Assays to determine serum levels of hepatitis E antibodies (IgG and IgM) will be performed at Emory's VTEU laboratory. Venous blood samples (approximately 10 mL) for antibody assays will be collected from each subject at screening and sent directly to Emory's VTEU laboratory for baseline testing. Seronegative samples will be defined as per the Wantai HEV-IgM and IgG ELISA package inserts (A/C.O. <0.9).

Venous blood samples (approximately 10 mL) will be collected immediately prior to each study vaccination (Days 1, 29, and 180) and Days 8, 15, after each study vaccination (Days 8, 15, 36, 43, 187, 194), Day 29 after each boost vaccination (Days 57 and 208), and Day 360. Subjects who withdraw early will have hepatitis E antibody assays run on available sera. Samples for immunogenicity assessments will be shipped from the DMID CMS to Emory's VTEU laboratory for vaccine immunogenicity assessments beginning with the completion of the Day 360 visit.

Seroconversion will be defined as a change from a seronegative result to a seropositive result as defined by the Wantai HEV-IgM and IgG ELISA package inserts (A/C.O. >1.1). As defined by prior studies,[24] the antibody concentration in samples negative for hepatitis E virus IgG was set at 0.0385 Wu/mL which was half the lower limit of quantification. A 4-fold seroconversion will be defined as a HEV IgG ≥0.154 in a subject that was HEV seronegative at Day 1.

Immunogenicity will be assessed by serum immune responses:

- Serum will be separated from blood samples collected on Days 1, 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360 and HEV IgG and IgM will be determined by ELISA.

5. SAMPLE SIZE CONSIDERATIONS

The sample size for this study was selected to obtain preliminary estimates of HEV-239 vaccine safety and immunogenicity in a time sensitive manner.

Given an N of 20 vaccinees, there is an ~88% probability of detecting an adverse event occurring in 10% of the population and a ~99% probability of detecting an adverse event occurring in 20%. Placebo subjects are included in order to reduce observer bias and are not intended to be a comparison group. Probabilities of observing at least one adverse event for a given true event rate are presented in the Table 2.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order HEV-239, Placebo and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

6.2. Timing of Analyses

The final analysis will be performed after database lock. No interim analysis is planned.

6.3. Analysis Populations

6.3.1. Modified Intention-to-Treat (mITT) Population

The modified intent-to-treat (mITT) population includes all subjects who received at least one study vaccination and contributed both pre- and at least one post-study vaccination blood sample for immunogenicity testing for which valid results were reported. Subjects will be analyzed according to the study arm to which they were randomized.

6.3.2. Per Protocol Population

The per protocol (PP) population includes all subjects in the mITT subset with the following exclusions:

- Data from all available visits for subjects found to be ineligible at baseline.
- Data from all visits subsequent to major protocol deviations, such as:
  - Second or third study vaccination not received,
  - Receipt of non-study licensed live vaccine within 30 days prior to or after each study vaccination,
  - Receipt of non-study licensed inactivated vaccine within 14 days prior to or after each study vaccination,
  - Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days prior to or after each study vaccination.
- Data from any visit that occurs substantially out of window.
- In the case of mis-randomization, subjects will be analyzed according to the study product received.

6.3.3. Safety Population

The Safety Analysis population includes all subjects who received at least one study vaccination.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

6.5. Missing Data

All attempts will be made to collect all data per protocol. As missing data are expected to be minimal, no imputation will be performed for missing values. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses will be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

6.6. Interim Analyses and Data Monitoring

Safety Review

The Safety Monitoring Committee (SMC) will review study progress and subject clinical, safety, and reactogenicity data at the following time points:

- The SMC will be provided with top line safety data through Day 57 for all participants.
- Final review meeting: 6 to 8 months after clinical database lock to review the cumulative unblinded safety and efficacy data for this trial. The data will be provided in a standard summary format. The SMC may be asked to provide recommendations in response to questions posed by DMID.
- Ad hoc when a halting rule is met, for immediate concerns regarding observations during this trial, or as needed.

Study Halting Criteria

Further enrollment and study vaccinations will be halted for SMC review/recommendation if any of the following are reported:

- Any subject experiences ulceration, abscess, or necrosis at the injection site related to study vaccination.
- Two or more subjects who have received at least one dose of study vaccine to date experience the same, at Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) level, severe (grade 3) study vaccine-related unsolicited adverse event.
- Two or more subjects who have received at least one dose of study vaccine to date experience a severe (grade 3) study vaccine-related laboratory adverse event in the same laboratory parameter.
- Two or more subjects who have received at least one dose of study vaccine to date experience the same severe (grade 3) solicited injection site adverse event that persists for 3 or more days and does not resolve or decrease to a lower grade (The size [measured in mm] of ecchymosis, erythema and induration/swelling will not be used as a halting criterion).
- Two or more subjects who have received at least one dose of study vaccine to date experience the same severe (grade 3) study vaccine-related solicited systemic adverse event that persists for 3 or more days and does not resolve or decrease to a lower grade (Subjective systemic reaction corroborated by study personnel).
- Any subject experiences a study vaccine-related laryngospasm, bronchospasm, or anaphylaxis within 1 day of study vaccination.
- Any subject experiences a study vaccine-related allergic reaction (e.g., generalized urticaria) within 3 days of study vaccination.

- Any subject experiences a study vaccine-related SAE from the time of the first study vaccination through the subject's last study visit.

Individual Halting Criteria

Individual subjects will not be administered boost vaccination doses (2nd or 3rd vaccination) if he or she experiences ANY of the following:

- Anaphylaxis within 1 day after administration of a study vaccine.
- Allergic reaction (e.g., generalized urticaria) within 3 days after administration of a study vaccine.
- A serious adverse event (SAE) that is considered to be study vaccine-related.
- A severe (grade 3) laboratory adverse event that is considered to be study vaccine-related and persists for 3 or more days.
- A severe (grade 3) unsolicited adverse event that is considered to be study vaccine-related and does not resolve or decrease to a lower grade.

These interim analyses will not involve testing of a hypothesis. In no case will the trial be prematurely terminated based on testing a hypothesis concerning the outcomes of interest.

6.7. Multicenter Studies

Not applicable. This study will take place at a single Vaccine Treatment and Evaluation Unit (VTEU).

6.8. Multiple Comparisons/Multiplicity

This study was not designed to test any specific null hypothesis, and as such no adjustments for multiple testing are planned.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Table 11 presents a summary of the reasons that subjects were screened but not enrolled.

The composition of analysis populations, including reasons for subject exclusion, by treatment arm, is presented in Table 9. Excluded subjects are listed in Listing 4.

The disposition of subjects in the study will be tabulated by treatment group (Table 8). The table shows the total number of subjects screened, enrolled, receiving at least 1 dose, receiving at least 2 doses, discontinued dosing or terminated from study follow-up and the number completing the study.

A flowchart showing the disposition of study subjects, adapted from the Consort Statement [12] will be included (Figure 2). This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed, by treatment arm.

A listing of subjects who discontinued dosing or terminated from study follow-up and the reason will be included in Listing 1.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and treatment group for all subjects (Table 3). Deviations that are considered major deviations that will be reviewed for possible subject exclusion from the per protocol population include: second or third study vaccination not received, receipt of non-study licensed live vaccine within 30 days prior to or after a study vaccination, receipt of non-study licensed inactivated vaccine within 14 days prior to or after a study vaccination, and receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days prior to or after a study vaccination. All subject-specific protocol deviations and non-subject specific protocol deviations will be included as data listings (Listing 2 and Listing 3, respectively).

8. IMMUNOGENICITY EVALUATION

All immunogenicity variables will be listed by treatment group, subject, and visit (Listing 7). N, Geometric Mean, Standard Deviation, Minimum and Maximum will summarize continuous immunogenicity variables, whereas number and percent will summarize categorical immunogenicity variables. This study was not designed to test a specific null hypothesis, rather the primary objectives included assessing the safety and immunogenicity of HEV-239 vaccine administered via intramuscular injection.

Immunogenicity data summaries and analysis will be presented for the mITT and PP populations.

Immune response will be presented graphically using reverse cumulative distribution (RCD) curves (Figure 3, Figure 4, Figure 5, and Figure 6), and longitudinal presentation of GMCs (Figure 7, Figure 8, Figure 9, and Figure 10).

8.1. Primary Immunogenicity Analysis

HEV IgG by ELISA

The number and percentage of subjects showing ≥4-fold rise from the baseline in serum HEV IgG concentration determined by ELISA will be presented with exact (Clopper-Pearson) two-sided 95% CI by study arm at Days 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360 (Table 19 and Table 20).

8.2. Secondary Immunogenicity Analyses

HEV IgG by ELISA

The number and percentage of subjects with seroconversion (defined as crossing the threshold from negative to positive) from baseline in serum HEV IgG determined by ELISA will be presented with exact (Clopper-Pearson) two-sided 95% CI by study arm at Days 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360 (Table 23 and Table 24). GMCs and corresponding 95% confidence intervals will be reported (Table 15 and Table 16).

HEV IgM by ELISA

The number and percentage of subjects with seroconversion (defined as crossing the threshold from negative to positive) from baseline in serum HEV IgM determined by ELISA will be presented with exact (Clopper-Pearson) two-sided 95% CI by study arm at Days 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360 (Table 21 and Table 22). GMCs and corresponding 95% confidence intervals will be reported (Table 17 and Table 18).

8.3. Exploratory Immunogenicity Analyses

Not applicable.

9. SAFETY EVALUATION

Safety listings will be sorted by treatment group, subject, and timepoint. N, Mean, Standard Deviation, Minimum and Maximum will summarize continuous safety variables, whereas number and percent will summarize categorical safety variables. Safety data will be summarized for the Safety Analysis Population. Subjects receiving a vaccination according to a study arm other than the study arm to which they were randomized, will be analyzed according to the vaccination they actually received.

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, ethnicity, and race will be presented by treatment group and overall (Table 12 and Table 13). Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with National Institutes of Health (NIH) reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the eCRF as "No" to each racial option.

Individual subject listings (Appendix 3) will be presented for all demographics (Listing 5); pre-existing medical conditions (Listing 6); vital signs and oral temperature (Listing 13); and concomitant medications (Listing 15).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 22.0 or higher.

Summaries of subjects' pre-existing medical conditions will be presented by treatment group (Table 14).

Individual subject listings will be presented for all medical conditions (Listing 6).

9.1.2. Prior and Concomitant Medications

Summaries of medications that were started prior to dosing and continuing at the time of dosing will be presented by WHO Drug Terms 2 and 3 and treatment group (Table 78).

Individual subject listings will be presented for all concomitant medications (Listing 15).

9.2. Measurements of Treatment Compliance

The number of doses of study product administered to subjects will be presented by treatment group as part of the subject disposition table (Table 8).

Table 10 presents the number of subjects who received first dose, by treatment arm.

9.3. Adverse Events

When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the total number of subjects in the safety population or the number of subjects in the safety population who received a given dose, first dose, second dose, or third dose as appropriate. All adverse events reported will be included in the summaries and analyses.

An overall summary of adverse events is presented in Table 25.

9.3.1. Solicited Events and Symptoms

Systemic solicited adverse events were collected pre-vaccination, and systemic and local solicited adverse events were collected 30 minutes post-vaccination and then daily for 7 days after each vaccination and graded on a scale of 0 (absent), 1 (mild), 2 (moderate) and 3 (severe). The grading scales are presented in Table 4 and Table 5. Systemic events include: arthralgia, fever, feverishness, fatigue, headache, malaise, myalgia, nausea, and vomiting. Local events include: ecchymosis severity and measurement, erythema measurement, induration/swelling severity and measurement, pain, pruritus, and tenderness.

The proportion of subjects reporting at least one solicited adverse event will be summarized for each solicited adverse event, any systemic symptom, any local symptom, and any symptoms. The 95% confidence interval (CI) calculated using Clopper-Pearson methodology from a binomial distribution (SAS Proc Freq with a binomial option) will be presented (Table 27).

For each systemic and local event, any systemic event, any local event, and any solicited event, the maximum severity over 7 days after each vaccination will be summarized for the Safety population. The number and percentage of subjects reporting each event will be summarized by the maximum severity and treatment group, separately for each vaccination and over all vaccinations. For each event the denominator is the number of subjects with non-missing data for the specific event (Table 28).

The number of subjects reporting a solicited adverse event will be summarized for each day post vaccination for each vaccination and for all vaccinations combined both in a summary table (Table 29, Table 30, Table 31, Table 32, Table 33, Table 34, Table 35, and Table 36) and graphically in a bar chart (Figure 11, Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, Figure 17, and Figure 18). A comparison of the event rate for each treatment group between vaccination 1 and vaccination 3 will be presented (Table 37). The duration of solicited adverse events will be summarized by dose number and treatment group (Table 38).

Solicited adverse events by subject will be presented in Listing 8 and Listing 9.

9.3.2. Unsolicited Adverse Events

The proportion of subjects reporting at least one unsolicited adverse event will be summarized by MedDRA system organ class and preferred term for each vaccination and over all vaccinations. Denominators for percentages are the number of subjects who received the vaccination being summarized.

Adverse events by subject will be presented in Listing 10.

The following summaries for unsolicited adverse events will be presented by MedDRA system organ class, preferred term, vaccination and treatment group:

- Summary of adverse events occurring in 5% of subjects (Table 26);
- Subject incidence and total frequency of adverse events over time with 95% CI (Day 1-8, Day 9-29 (pre-vaccination), Day 29 (post-vaccination)-36, Day 37-57, Day 180-187, Day 188-208, Day 209-360, and anytime post-any dose) (Table 39 and Table 40);
- Summary of severity and relationship to study product (Table 41);
- Subject incidence and total frequency of related adverse events over time (Day 1-8, Day 9-29(pre-vaccination), Day 29 (post-vaccination)-36, Day 37-57, Day 180-187, Day 188-208, Day 209-360, and anytime post-any dose) (Table 42 and Table 43);
- Subject listing of non-serious adverse events of moderate or greater severity (Table 45);

- Bar chart of the frequency of serious and non-serious related adverse events by severity and MedDRA system organ class (Figure 19);
- Bar chart of the incidence of serious and non-serious related adverse events by maximum severity and MedDRA system organ class (Figure 20);

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

The following listings will be presented including Subject ID, Adverse Event Description, Last Dose Received/Days Post Dose, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days):

- Deaths and Serious Adverse Events (Table 44);

9.5. Pregnancies

For any subjects in the Safety population who become pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A table summarizing the total pregnancies, number of live births, and number of spontaneous abortions, elective abortions or still births by treatment will be presented. In addition, a listing of pregnancies and outcomes will be presented (Listing 16, Listing 17, Listing 18, Listing 19, and Listing 20).

9.6. Clinical Laboratory Evaluations

Clinical safety laboratory parameters will be collected at Baseline (screening visit) and Study Days 8, 36, 180, and 187. If indicated by symptoms they may also be evaluated at Study Day 15, 43, 194 or at Early Termination/Unscheduled visits.

Chemistry parameters to be evaluated include creatinine and alanine aminotransferase (ALT). Hematology parameters to be evaluated include white blood cell count (WBC), absolute neutrophil count (ANC), the absolute eosinophil count (AEC), hemoglobin, and platelets. Grading scales for safety laboratory parameters are presented in Table 6.

The distribution of laboratory results by severity, time point, and treatment group will be presented in Table 48, Table 49, Table 50, Table 51, Table 52, and Table 53 for chemistry and beginning at Table 56 and concluding at Table 67 for hematology. Descriptive statistics including mean, standard deviation, median, minimum and maximum values by time point, for each laboratory parameter, will be summarized in Table 54, Table 55, Table 68, Table 69, Table 70, Table 71, and Table 72. Changes in laboratory values will be presented in Figure 21, Figure 22, Figure 23, Figure 24, Figure 25, Figure 26, and Figure 27.

Subject visits with abnormal laboratory results, Grade 1 severity or higher, will be presented in Table 46 and Table 47.

Listing 11 and Listing 12 will provide a complete listing of individual clinical laboratory results with applicable reference ranges.

9.7. Vital Signs and Physical Evaluations

Vital sign measurements include pulse, systolic blood pressure, diastolic blood pressure and oral temperature. Vital signs are assessed at Day 1, Day 8, Day 15, Day 29, Day 36, Day 43, Day 180, Day 187, and Day 194. Vital signs will be tabulated by visit, treatment group, and maximum severity (Table 73, Table 74, Table 75,

Table 76, and Table 77) and listed by subject (Listing 13). The vital signs grading scale is presented in Table 7.

Physical Examinations are performed only at screening and where indicated based upon timing and/or symptoms at follow-up visits. Such indicated physical examinations, if performed, will be presented in Listing 14. Physical Examinations will include assessments of the following organs and organ systems: skin, head, eyes, ears, nose, and throat, neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the eCRFs. A by-subject listing of concomitant medication use will be presented (Listing 15). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group for the Safety population (Table 78).

9.9. Other Safety Measures

Not applicable.

10. PHARMACOKINETICS

Not applicable.

11. IMMUNOGENICITY

See Section 8.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001" The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1%"; values greater than 99% but less than 100% will be reported as ">99%". Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14. TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Not applicable.

16. REFERENCES

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17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.5.1 Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 1: Schedule of Study Procedure

Study Visit	**Screening**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Study day from 1st vaccine	Screening (≤28 days)[a,b]	Day 1[c]	Day 4** +/-1	Day 8 +/-1	Day 15 +/-2	Day 29 +/-2	Day 32**	Day 36	Day 43	Day 57	Day 120**	Day 180 +/- 14	Day 184 **	Day 187	Day 194	Day 208	Day 270**	Day 360 +/-28	Early Termination/ Unscheduled
Study day from 2nd vaccine						Day 1	Day 4** +/-1	Day 8 +/-1	Day 15 +/-2	Day 29 +/-2	Day 92** +/- 14								
Study day from 3rd vaccine												Day 1	Day 4** +/-1	Day 8 +/-1	Day 15 +/-2	Day 29 +/-2	Day 90** +/-14	Day 180 +/- 14	
Obtain Informed Consent	X[b]																		
Medical History*	X	X				X						X							
Serum pregnancy test[e]	X																		
Urine pregnancy test[e]		X[h]				X[h]						X[h]							{X}
Review of birth control history with female subjects	X	X[e]				X[e]						X[e]							X
Counsel on pregnancy avoidance[e]	X	X		X	X	X		X	X	X	X	X		X	X	X			{X}
Physical examination [i]	X	{X}[h]		{X}	{X}	{X}[h]		{X}	{X}	{X}		{X}[h]		{X}	{X}	{X}		{X}	{X}
Vital signs[j]	X	X		X	X	X		X	X			X		X	X				{X}
Review of Eligibility Criteria	X	X[c,h]				X[h]						X[h]							
Study Visit	**Screening**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	

Study Visit	**Screening**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Study day from 1st vaccine	Screening (≤28 days)[a,b]	Day 1[c]	Day 4** +/-1	Day 8 +/-1	Day 15 +/-2	Day 29 +/-2	Day 32**	Day 36	Day 43	Day 57	Day 120**	Day 180 +/- 14	Day 184**	Day 187	Day 194	Day 208	Day 270**	Day 360 +/-28	Early Termination/ Unscheduled
Study day from 2nd vaccine						Day 1	Day 4** +/-1	Day 8 +/-1	Day 15 +/-2	Day 29 +/-2	Day 92** +/- 14								
Study day from 3rd vaccine												Day 1	Day 4** +/-1	Day 8 +/-1	Day 15 +/-2	Day 29 +/-2	Day 90** +/-14	Day 180 +/- 14	
Pre-Administration Reactogenicity Assessments		X[h]				X[h]						X[h]							
Randomization		X[h]																	
Study vaccine administration		▲				▼						▼							
Distribution of memory aid		X[k]				X[k]						X[k]							
Review of subject diary/ solicited events by staff			X	X	X		X	X	X				X	X	X				{X}
AE/SAE Assessment[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	{X}
Evaluate vaccination site		X		X	{X}	X		X	{X}			X		X	{X}				{X}
Post-Administration Reactogenicity Assessments		X				X						X							
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X[l]	X	X	X	X	X	X[l]	X[l]	X[l]
Hematology, chemistry[f] (mL)	13[n]			13	{13}			13	{13}			13[h]		13	{13}				{13}

Study Visit	Screening	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	
Hepatitis B surface antigen, hepatitis C antibody, HIV types 1 and 2 antigen/antibody	10																		
Urine drug screen	X																		
Hepatitis E IgM and IgG antibodies	10																		
Serum: Immunogenicity (mL)		10[h]		10	10	10[h]		10	10	10		10[h]		10	10	10		10	{10}
Study Visit	**Screening**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Study day from 1[s] vaccine	Screening (≤28 days)[a,b]	Day 1[c]	Day 4** +/-1	Day 8 +/-1	Day 15 +/-2	Day 29 +/-2	Day 32**	Day 36	Day 43	Day 57	Day 120**	Day 180 +/- 14	Day 184 **	Day 187	Day 194	Day 208	Day 270**	Day 360 +/-28	Early Termination/ Unscheduled
Study day from 2[nd] vaccine						Day 1	Day 4** +/-1	Day 8 +/-1	Day 15 +/-2	Day 29 +/-2	Day 92** +/- 14								
Study day from 3[rd] vaccine												Day 1	Day 4** +/-1	Day 8 +/-1	Day 15 +/-2	Day 29 +/-2	Day 90** +/-14	Day 180 +/- 14	
Peripheral Blood Mononuclear Cells (PBMC) and Plasma Collection for Future Use		48[h]		16	36	48[h]		16	36	32		48[h]		16	36	32		32	{≤48}
Total Blood Volume per visit (mL)[n]	33	58		39	{59}	58		39	{59}	42		71		39	{59}	42		42	{71}
Cumulative Blood Volume [n]	33	91		130	{189}	247		286	{345}	387		458		497	{556}	598		640	

Study Visit	Screening	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	

▲Prime dose: HEV 239 or Placebo**;** ▼Boost dose: HEV 239 or Placebo;

NOTE 1: In case of early withdrawal due to an adverse event, the investigator will collect all information relevant to the AE and safety of the subject, and will follow the subject to resolution, or until reaching a clinically stable endpoint. If feasible, blood will be drawn for immunologic assays. Subjects who wish to withdraw consent will be offered an optional visit for safety follow-up (before the formal withdrawal of consent). The subject has the right to refuse.

a) Screening may be split into multiple days or visits. This will include collection of baseline demographics and subject contact information.

b) Signing of the informed consent form (ICF) needs to be done before the first study-related activity.

c) The investigators should ensure that all study enrollment criteria have been met at the end of the screening period. If a subject's status changes (including laboratory results or the receipt of additional medical records) after screening but before Day 1 such that the subject no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

d) Pre-study medications and therapies will be reviewed and recorded for the 30 days prior to the start of screening.

e) Subjects will be counselled to use adequate birth control methods to avoid pregnancy.

f) Baseline laboratories include complete blood count with differential (which will include white blood cells, absolute neutrophil count (ANC), absolute eosinophil count (AEC), hemoglobin, and platelets), creatinine, glucose, Alanine aminotransferase (ALT), hepatitis B surface antigen, hepatitis C antibody, HIV types 1 and 2 antigen/antibody, hepatitis E IgM and IgG antibodies, and urine drug screen (Protocol Section 2.3.1). Retesting of values that lead to exclusion is allowed once using an unscheduled visit during the screening period, provided there is an alternative explanation for the out of range value. If the initial laboratory screening occurred more than 28 days before baseline (Day 1) but the subject was unable to be vaccinated within the 28-day window (e.g., due to meeting Exclusion Criteria), the subject must have safety laboratories repeated (see protocol-specific Manual of Procedures (MOP) for details). Safety laboratories will be obtained on Days 8, 36, 180, and 187 will include complete blood count with differential (which will include white blood cells, ANC, AEC, hemoglobin, and platelets), Cr, and ALT (Protocol Section 2.3.1).

h) Prior to study vaccine administration.

i) An abbreviated physical examination will be carried out at screening. At other visits, symptom-directed examination will be performed as indicated by the investigator.

j) Includes heart rate, blood pressure and oral body temperature after at least 5 minutes rest. To be assessed prior to study vaccine administration and at a minimum of 30 minutes after study vaccine administration. At screening this will also include height and body weight for determination of body mass index (BMI).

k) When the memory aid is distributed to subjects, they will also be instructed as to when to contact the investigator about unsolicited AEs. Hypersensitivity symptoms will also be reviewed with the subject and they will be counselled that if any of these were occur they must contact study personnel or seek medical attention immediately.

l) Concomitant therapies between D57 and D150 and from D208 – D360 should only be recorded if administered in conjunction with SAEs.

m) Solicited AEs: Inclusive of solicited injection site reactions and systemic reactogenicity events performed on the day of each study vaccination through at least D8 after each study vaccination (see Protocol Sections 8.1.2). Unsolicited AEs: Collection of unsolicited AEs from time of first vaccination through D57; then from Day 180 – 208. SAEs: SAEs will be collected from the time of the first study vaccination through the last study visit (Day 360).

n) Volumes are the maximum volumes expected to be drawn. Samples may be fasted or non-fasted. The total volume at an unscheduled or early termination visit will not exceed the individual time point volume.

{ } If indicated based upon timing and/or symptoms.

* See Protocol Section 7.1.1 regarding details of medical history to be collected.

** Telephone Visit

9.7.1 Sample Size

Table 2: Probability (%) of Observing at Least One Adverse Event

Adverse Event Frequency	**N = 20**
0.01% Rare	0.20
0.1% Uncommon	1.98
1% Common	18.21
10% Very Common	87.84
20% Very Common	98.85

10.2 Protocol Deviations

Table 3: Distribution of Protocol Deviations by Category, Type, and Treatment Group

Category	Deviation Type	HEV-239 (N=X)		Placebo (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type						
	Did not meet inclusion criterion	x	x	x	x	x	x
	Met exclusion criterion						
	ICF not signed prior to study procedures						
	Other						
Treatment administration schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Missed treatment administration						
	Delayed treatment administration						
	Other						
Follow-up visit schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Other						
Protocol procedure/assessment	Any type						
	Incorrect version of ICF signed						
	Blood not collected						
	Urine not collected						
	Stool not collected						
	Other specimen not collected						
	Too few aliquots obtained						
	Specimen result not obtained						
	Required procedure not conducted						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Specimen temperature excursion						
	Other						
Treatment administration	Any type						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Other						
Blinding policy/procedure	Any type						
	Treatment unblinded						
	Other						

Note: N= Number of subjects enrolled

12.2.2 Displays of Adverse Events

Table 4: Solicited Adverse Event Grading Scale – Local (Injection Site) Reactogenicity Grading

Local (Injection Site) Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain – experienced without touching the injection site (spontaneous discomfort)	No pain medication or it requires use of a non-narcotic pain reliever ≤24hours OR does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours OR interferes with activity	Any use of narcotic pain reliever OR prevents daily activity
Tenderness – hurts only when injection site is touched or the arm is moved	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Pruritus (Itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising) Severity[a]	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Induration (Hardness)/Swelling Severity[a]	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising) Measurement[b]	25mm – 50mm	51 mm – 100mm	>100 mm
Erythema (Redness) Measurement[b]	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Induration (Hardness)/Swelling Measurement[b]	25 mm – 50 mm	51 mm – 100 mm OR interferes with activity	>100 mm OR prevents daily activity

[a] Will also be measured in mm but size will not be used as halting criteria.
[b] Will not be used as halting criteria.

Table 5: Solicited Adverse Event Grading Scale – Systemic Reactogenicity Grading

Systemic	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Feverishness (Chills/Shivering/Sweating)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Fatigue (Tiredness)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Malaise (General Unwell Feeling)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Myalgia (Body Aches/Muscular Pain)[a]	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Arthralgia (Joint Pain)[a]	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Headache	No interference with daily activity	Repeated use of non-narcotic pain reliever >24 hours OR some interference with activity	Significant; any use of narcotic pain reliever OR prevents daily activity OR requires triptans
Nausea	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity or requires IV hydration
Fever[b] – oral	38.0°C – 38.4°C 100.4°F – 101.1°F	38.5°C – 38.9°C 101.2°F – 102.0°F	>38.9°C >102.0°F

[a] Not at injection site.
[b] A fever can be considered not related to the study product if an alternative etiology can be documented

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 6: Laboratory Adverse Event Grading Scale

Laboratory Adverse Events				
Blood, Serum, or Plasma	**Normal Range**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Creatinine – mg/dL (Female)	0.5 – 1.10	≥1.11 – 1.79	≥1.80-2.09	≥2.10
Creatinine – mg/dL (Male)	0.6 – 1.35	≥1.36 – 1.79	≥1.80-2.09	≥2.10
ALT U/L (Female)	6 – 29	30 – 105	106-175	>175
ALT U/L (Male)	9 – 46	47 – 105	106-175	>175
Hemoglobin (Female) - g/dL	11.7 – 15.5	11.0-11.6	9.5-10.9	<9.5
Hemoglobin (Male) - g/dL	13.2 – 17.1	12.0 – 13.1	10.0 – 11.9	<10.0
WBC Increase (Thousand/uL)	3.8 – 10.8	10.9 – 15.0	15.1 – 20.0	> 20.0
WBC Decrease (Thousand/uL)	3.8 – 10.8	2.5-3.7	1.5-2.4	<1.5
Absolute Neutrophil Count Decrease (cells/uL)	1500 – 7800	1490 – 1499	1000-1489	<1000
Absolute Eosinophil Count Increase (cells/uL)	15 – 500	501-749	750-1500	>1500
Platelets Decreased (Thousand/uL)	140 – 400	120-139	100-119	<100

Table 7: Vital Signs Adverse Event Grading Scale

Vital Sign	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C) [1]	38.0 – 38.4	38.5 – 38.9	≥39.0
Tachycardia - beats per minute	101 – 115	116 – 130	>130 or ventricular dysrhythmias
Bradycardia - beats per minute	45 - 50 bpm	40 – 44 bpm	<40 bpm
Hypertension (systolic)- mm Hg[2]	141-150	151-160	>160
Hypertension (diastolic) - mm Hg[2]	91-95	96-100	>100
Hypotension (systolic) - mm Hg[2]	85-89	80-84	< 80
Hypotension (diastolic) – mm Hg[2]	50 – 54	45 – 49	<45

[1] Oral temperature; no recent hot or cold beverages or smoking.
[2] Assuming subject is awake, and resting for AEs; 3 measurements on the same arm with concordant results.

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 8: Subject Disposition by Treatment Group

Subject Disposition	HEV-239 (N=X)		Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100
Received Dose 1	x	xx	x	xx	x	xx
Received Dose 2	x	xx	x	xx	x	xx
Received Dose 3	x	xx	x	xx	x	xx
Completed Final Blood Draw						
Completed Follow-up (Study Day 360)[a]						
Completed Per Protocol[b]						

Note: N=All subjects
[a] Refer to Listing 16.2.1 for reasons subjects discontinued or terminated early.
[b] Refer to Listing 16.2.3 for reasons subjects are excluded from the Analysis populations.

Table 9: Analysis Populations by Treatment Group

Analysis Populations	Reason Subjects Excluded	HEV-239 (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
Safety Population	Any Reason	x	xx	x	xx	x	xx
	Did not receive study product						
Modified Intent-to-Treat Population	Any Reason						
	No pre-vaccination serum results						
	No post-vaccination serum results						
Per Protocol Population	Any Reason						
	Ineligible at baseline						
	Did not receive all 3 doses						
	Received non-study licensed vaccine						
	Received immunosuppressive therapy						

Note: N=All subjects enrolled

Table 10: Dates of First Treatment by Treatment Group

Dates of Dosing	HEV-239 (N=X)	Placebo (N=X)	All Subjects (N=X)
Total (Entire period of enrollment)			
DDMMMYYYY-DDMMMYYYY [categorize based on length of enrollment period]	x	x	x

Note: N=Number of subjects in the Safety Population

Table 11: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	xx
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Eligible but not enrolled		x	xx

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of screen failures.

14.1.2 Demographic Data by Study Group

Table 12: Summary of Categorical Demographic and Baseline Characteristics

Variable	Characteristic	HEV-239 (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx
	Female						
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino						
	Not Reported						
	Unknown						
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx
	Asian						
	Native Hawaiian or Other Pacific Islander						
	Black or African American						
	White						
	Multi-Racial						
	Unknown						

Note: N=Number of subjects in the Safety Population

Table 13: Summary of Continuous Demographic and Baseline Characteristics

Variable	Statistic	HEV-239 (N=X)	Placebo (N=X)	All Subjects (N=X)
Age (years)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x

Note: N=Number of subjects in the Safety Population

14.1.3 Prior and Concurrent Medical Conditions

Table 14: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group

MedDRA System Organ Class	HEV-239 (N=X)		Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx
[SOC 1]						
[SOC 2]						

Note: N=Number of subjects in the Safety Population; n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

14.2 Immunogenicity Data

Table 15: Serum HEV IgG GMC Results with 95% Confidence Intervals by Time Point and Treatment Group, mITT Population

Time Point	Statistic	HEV-239 (N=X)	Placebo (N=X)
Day 1 (Dose 1)	n	x	x
	GMC	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x
	[Min, Max]	[x.x, x.x]	[x.x, x.x]
Day 8	n		
	GMC		
	95% CI		
	[Min, Max]		
Day 15	n		
	GMC		
	95% CI		
	[Min, Max]		
Day 29 (Dose 2)	n		
	GMC		
	95% CI		
	[Min, Max]		
Day 36	n		
	GMC		
	95% CI		
	[Min, Max]		
Day 43	n		
	GMC		
	95% CI		
	[Min, Max]		
Day 57	n		
	GMC		
	95% CI		
	[Min, Max]		
Day 180 (Dose 3)	n		
	GMC		
	95% CI		
	[Min, Max]		
Day 187	n		

Time Point	Statistic	HEV-239 (N=X)	Placebo (N=X)
	GMC		
	95% CI		
	[Min, Max]		
Day 194	n		
	GMC		
	95% CI		
	[Min, Max]		
Day 208	n		
	GMC		
	95% CI		
	[Min, Max]		
Day 360	n		
	GMC		
	95% CI		
	[Min, Max]		

Note: N= Number of subjects in the mITT Population; n=Subjects with results at visit

Tables with similar format:

Table 16: Serum HEV IgG GMC Results with 95% Confidence Intervals by Time Point and Treatment Group, Per Protocol Population

Table 17: Serum HEV IgM GMC Results with 95% Confidence Intervals by Time Point and Treatment Group, Per Protocol Population

Table 18: Serum HEV IgM GMC Results with 95% Confidence Intervals by Time Point and Treatment Group, Per Protocol Population

Table 19: Serum HEV IgG GMFR and Seroresponse (4-Fold Rise) Results by Time Point and Treatment Group, mITT Population

Time Point	Statistic	HEV-239 (N=X)	Placebo (N=X)
Day 8	n	x	x
	GMFR[a]	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x
	4-Fold Rise[b]	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x
Day 15	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		
	95% CI		
Day 29 (Dose 2)	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		
	95% CI		
Day 36	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		
	95% CI		
Day 43	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		
	95% CI		
Day 57	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		
	95% CI		
Day 180 (Dose 3)	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		

Time Point	Statistic	HEV-239 (N=X)	Placebo (N=X)
	95% CI		
Day 187	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		
	95% CI		
Day 194	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		
	95% CI		
Day 208	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		
	95% CI		
Day 360	n		
	GMFR[a]		
	95% CI		
	4-Fold Rise[b]		
	95% CI		

Note: N=Number of subjects in the mITT Population; n=Subjects with results at visit
[a] GMFR represents the geometric mean fold rise in antibody compared to pre-dose 1.
[b] 4-Fold Rise represents the percentage of subjects with at least a 4-Fold Rise in antibody compared to pre-dose 1.

Tables with similar format:

Table 20: Serum HEV IgG GMFR and Seroresponse (4-Fold Rise) Results by Time Point and Treatment Group, Per Protocol Population

Table 21: Serum HEV IgM GMFR and Seroconversion Results by Time Point and Treatment Group, mITT Population

Time Point	Statistic	HEV-239 (N=X)	Placebo (N=X)
Day 8	n	x	x
	GMFR[a]	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x
	Seroconversion[b]	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x
Day 15	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		
Day 29 (Dose 2)	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		
Day 36	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		
Day 43	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		
Day 57	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		
Day 180 (Dose 3)	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		

Time Point	Statistic	HEV-239 (N=X)	Placebo (N=X)
Day 187	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		
Day 194	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		
Day 208	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		
Day 360	n		
	GMFR[a]		
	95% CI		
	Seroconversion[b]		
	95% CI		

Note: N=Number of subjects in the mITT Population; n=Subjects with results at visit
[a] GMFR represents the geometric mean fold rise in antibody compared to pre-dose 1.
[b] Seroconversion represents the percentage of subjects with a change from a seronegative result at pre-dose 1 to a seropositive result.

Tables with similar format:

Table 22: Serum HEV IgM GMFR and Seroconversion Results by Time Point and Treatment Group, Per Protocol Population

Table 23: Serum HEV IgG Seroconversion Results by Time Point and Treatment Group, mITT Population

Time Point	Statistic	HEV-239 (N=X)	Placebo (N=X)
Day 8	n	x	x
	Seroconversion[a]	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x
Day 15	n		
	Seroconversion[a]		
	95% CI		
Day 29 (Dose 2)	n		
	Seroconversion[a]		
	95% CI		
Day 36	n		
	Seroconversion[a]		
	95% CI		
Day 43	n		
	Seroconversion[a]		
	95% CI		
Day 57	n		
	Seroconversion[a]		
	95% CI		
Day 180 (Dose 3)	n		
	Seroconversion[a]		
	95% CI		
Day 187	n		
	Seroconversion[a]		
	95% CI		
Day 194	n		
	Seroconversion[a]		
	95% CI		
Day 208	n		
	Seroconversion[a]		
	95% CI		
Day 360	n		
	Seroconversion[a]		
	95% CI		

Note: N=Number of subjects in the mITT Population; n=Subjects with results at visit
[a] Seroconversion represents the percentage of subjects with a change from a seronegative result at pre-dose 1 to a seropositive result.

Tables with similar format:

Table 24: Serum HEV IgG Seroconversion Results by Time Point and Treatment Group, Per Protocol Population

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 25: Overall Summary of Adverse Events

	HEV-239 (N = xx)		Placebo (N = xx)		All Subjects (N = xx)	
Subjects[a] with	n	%	n	%	n	%
At least one local solicited adverse event	x	x	x	x	x	x
At least one systemic solicited adverse event	x	x	x	x	x	x
At least one unsolicited adverse event	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x
At least one severe (Grade 3) unsolicited adverse event	x	x	x	x	x	x
Related	x	x	x	x	x	x
Not related	x	x	x	x	x	x
At least one clinical safety laboratory adverse event	x	x	x	x	x	x
At least one serious adverse event[b]	x	x	x	x	x	x
At least one related, serious adverse event	x	x	x	x	x	x
At least one adverse event leading to early termination[c]	x	x	x	x	x	x

N = Number of subjects in the Safety Population
[a] Subjects are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Table 43.
[c] As reported on the Adverse Event eCRF.

Table 26: Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - Safety Population

Preferred Term	MedDRA System Organ Class	HEV-239 (N=X)			Placebo (N=X)			All Subjects (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc.	Etc.									
Other (Non-serious) Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc	Etc									

N = number of subjects in the Safety Population (number of subjects at risk).
n= number of subjects reporting event.
Events= total frequency of events reported.

14.3.1.1 Solicited Adverse Events

Table 27: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Treatment Group

Symptom	Post Dose 1 HEV-239 (N=X)			Post Dose 1 Placebo (N=X)			Post Dose 2 HEV-239 (N=X)			Post Dose 2 Placebo (N=X)			Post Dose 3 HEV-239 (N=X)			Post Dose 3 Placebo (N=X)			Post Any Dose HEV-239 (N=X)			Post Any Dose Placebo (N=X)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
Any Systemic Symptom																								
Arthralgia																								
Fever																								
Feverishness																								
Fatigue																								
Headache																								
Malaise																								
Myalgia																								
Nausea																								
Vomiting																								
Any Local Symptom																								
Ecchymosis Severity																								
Ecchymosis Measurement																								
Erythema Measurement																								
Induration/Swelling Severity																								
Induration/Swelling Measurement																								
Pain																								
Pruritus																								
Tenderness																								

Note: N=Number of subjects in the Safety Population

Table 28: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group

Symptom	Severity	Post Dose 1 HEV-239 (N=X)			Post Dose 1 Placebo (N=X)			Post Dose 2 HEV-239 (N=X)			Post Dose 2 Placebo (N=X)			Post Dose 3 HEV-239 (N=X)			Post Dose 3 Placebo (N=X)			Post Any Dose HEV-239 (N=X)			Post Any Dose Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	None	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
	Mild																								
	Moderate																								
	Severe																								
Systemic Symptoms																									
Any Systemic Symptom	None	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
	Mild																								
	Moderate																								
	Severe																								
Arthralgia	None																								
	Mild																								
	Moderate																								
	Severe																								
Fever	None																								
	Mild																								
	Moderate																								
	Severe																								
Feverishness	None																								
	Mild																								
	Moderate																								
	Severe																								
Fatigue	None																								
	Mild																								

Table 28: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group *(continued)*

Symptom	Severity	Post Dose 1 HEV-239 (N=X)			Post Dose 1 Placebo (N=X)			Post Dose 2 HEV-239 (N=X)			Post Dose 2 Placebo (N=X)			Post Dose 3 HEV-239 (N=X)			Post Dose 3 Placebo (N=X)			Post Any Dose HEV-239 (N=X)			Post Any Dose Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
	Moderate																								
	Severe																								
Headache	None																								
	Mild																								
	Moderate																								
	Severe																								
Malaise	None																								
	Mild																								
	Moderate																								
	Severe																								
Myalgia	None																								
	Mild																								
	Moderate																								
	Severe																								
Nausea	None																								
	Mild																								
	Moderate																								
	Severe																								
Vomiting	None																								
	Mild																								
	Moderate																								
	Severe																								
Local Symptoms																									

Table 28: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group *(continued)*

Symptom	Severity	Post Dose 1 HEV-239 (N=X)			Post Dose 1 Placebo (N=X)			Post Dose 2 HEV-239 (N=X)			Post Dose 2 Placebo (N=X)			Post Dose 3 HEV-239 (N=X)			Post Dose 3 Placebo (N=X)			Post Any Dose HEV-239 (N=X)			Post Any Dose Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Local Symptom	None	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
	Mild																								
	Moderate																								
	Severe																								
Ecchymosis Severity	None																								
	Mild																								
	Moderate																								
	Severe																								
Ecchymosis Measurement	None																								
	Mild																								
	Moderate																								
	Severe																								
Erythema Measurement	None																								
	Mild																								
	Moderate																								
	Severe																								
Induration/Swelling Severity	None																								
	Mild																								
	Moderate																								
	Severe																								
Induration/Swelling Measurement	None																								

Table 28: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group *(continued)*

Symptom	Severity	Post Dose 1 HEV-239 (N=X)			Post Dose 1 Placebo (N=X)			Post Dose 2 HEV-239 (N=X)			Post Dose 2 Placebo (N=X)			Post Dose 3 HEV-239 (N=X)			Post Dose 3 Placebo (N=X)			Post Any Dose HEV-239 (N=X)			Post Any Dose Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
	Mild																								
	Moderate																								
	Severe																								
Pain	None																								
	Mild																								
	Moderate																								
	Severe																								
Pruritus	None																								
	Mild																								
	Moderate																								
	Severe																								
Tenderness	None																								
	Mild																								
	Moderate																								
	Severe																								

Note: N = Number of subjects in the Safety Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

Table 29: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – HEV-239, Post Dose 1

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Systemic Symptoms																					
Any Systemic Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Arthralgia	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Fever	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Feverishness	None																				
	Mild																				
	Moderate																				
	Severe																				

Table 29: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – HEV-239, Post Dose 1 *(continued)*

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Not Reported																				
Fatigue	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Headache	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Malaise	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Myalgia	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Nausea	None																				
	Mild																				
	Moderate																				
	Severe																				

Table 29: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – HEV-239, Post Dose 1 *(continued)*

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Not Reported																				
Vomiting	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Local Symptoms																					
Any Local Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Ecchymosis Severity	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Ecchymosis	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Erythema Measurement	None																				
	Mild																				
	Moderate																				

Table 29: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – HEV-239, Post Dose 1 *(continued)*

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Severe																				
	Not Reported																				
Induration/Swelling Severity	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Induration/Swelling Measurement	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Pain	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Pruritus	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Tenderness	None																				
	Mild																				
	Moderate																				

Table 29: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – HEV-239, Post Dose 1 *(continued)*

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Severe																				
	Not Reported																				

Note: N = Number of subjects in the Safety Population who received the specified dose. Severity is the maximum severity reported post dosing for each subject for each day.

Tables with similar format:

Table 30: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – Placebo, Post Dose 1

Table 31: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – HEV-239, Post Dose 2

Table 32: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – Placebo, Post Dose 2

Table 33: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – HEV-239, Post Dose 3

Table 34: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – Placebo, Post Dose 3

Table 35: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – HEV-239, Post Any Dose

Table 36: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Treatment Group – Placebo, Post Any Dose

Table 37: Number and Percentage of Subjects Experiencing Solicited Events for Dose 1 Compared with Dose 3 by Treatment Group

Treatment Group		Dose 3 – Subjects with No Symptoms	Dose 3 – Subjects with Mild or Greater Symptoms	Dose 3 – Total Number of Subjects
Systemic Symptom				
HEV-239	Dose 1 Subject with No Symptoms	x (%)	x (%)	x (%)
	Dose 1 Subjects with Mild or Greater Symptoms	x (%)	x (%)	x (%)
	Dose 1 Total Number of Subjects	x (%)	x (%)	x (100%)
Placebo	Dose 1 Subject with No Symptoms			
	Dose 1 Subjects with Mild or Greater Symptoms			
	Dose 1 Total Number of Subjects			
Local Symptoms				
HEV-239	Dose 1 Subjects with No Symptoms	x (%)	x (%)	x (%)
	Dose 1 Subjects with Mild or Greater Symptoms	x (%)	x (%)	x (%)
	Dose 1 Total Number of Subjects	x (%)	x (%)	x (100%)
Placebo	Dose 1 Subjects with No Symptoms			
	Dose 1 Subjects with Mild or Greater Symptoms			
	Dose 1 Total Number of Subjects			

Note: Denominators for percentages are the number of subjects in the Safety Population who received all three doses. [x] subjects did not get the second or third dose and are not included in this table.

Table 38: Duration of Symptoms Among Subjects Experiencing Solicited Events

Symptom	Post-Dose 1 Symptom Duration					Post-Dose 2 Symptom Duration					Post-Dose 3 Symptom Duration				
	n	Mean	Standard Deviation	Median	Min, Max	n	Mean	Standard Deviation	Median	Min, Max	n	Mean	Standard Deviation	Median	Min, Max
Any Symptom	xx	x.x	x.x	x.x	x, x	xx	x.x	x.x	x.x	x, x	xx	x.x	x.x	x.x	x, x
Systemic Symptoms															
Any Systemic Symptom	xx	x.x	x.x	x.x	x, x	xx	x.x	x.x	x.x	x, x	xx	x.x	x.x	x.x	x, x
Arthralgia															
Fever															
Feverishness															
Fatigue															
Headache															
Malaise															
Myalgia															
Nausea															
Vomiting															
Local Symptoms															
Any Local Symptom	xx	x.x	x.x	x.x	x, x	xx	x.x	x.x	x.x	x, x	xx	x.x	x.x	x.x	x, x
Ecchymosis Severity															
Ecchymosis															
Erythema Measurement															
Induration/Swelling Severity															
Induration/Swelling Measurement															
Pruritus															
Tenderness															

Note: n = Number of subjects in the Safety Population who received the specified dose and experienced the specified solicited symptom.

14.3.1.2 Unsolicited Adverse Events

Table 39: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Dose Number, and Treatment Group – HEV-239

MedDRA System Organ Class	MedDRA Preferred Term	Day 1-8 Post Dose 1 (N=X)				Day 9-29[a] Post Dose 1 (N=X)				Day 29[b]-36 Post Dose 2 (N=X)				Day 37-57 Post Dose 2 (N=X)				Day 180-187 Post Dose 3 (N=X)				Day 188-208 Post Dose 3 (N=X)				Day 209-360 Post Dose 3 (N=X)				Any Time[c] Post Any Dose (N=X)			
		n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events
Any SOC	Any PT	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x
[SOC 1]	Any PT																														
	[PT 1]																														
	[PT 2]																														
[SOC 2]	Any PT																														
	[PT 1]																														
	[PT 2]																														

Note: N = number of subjects in the Safety Population. This table presents number and percentage of subjects. A subject is only counted once per PT/time point.
a Day 29 prior to receiving Dose 2
b Day 29 after receiving Dose 2
c Includes all AEs collected Day 1 to Day 57 and Day 180 to Day 360 and SAEs collected from Day 57 to Day 180

Tables with similar format:

Table 40: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Dose Number, and Treatment Group – Placebo

Table 41: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group

MedDRA System Organ Class	Preferred Term	Severity	HEV-239 (N = X)						Placebo (N = X)						All Subjects (N = X)					
			Related		Not Related		Total		Related		Not Related		Total		Related		Not Related		Total	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	PT 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	PT 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Note: N = Number of subjects in the Safety Population.

Table 42: Related Unsolicited Adverse Events Post Dosing by MedDRA System Organ Class and Preferred Term, Dose, and Treatment Group – HEV-239

		Day 1-8 Post Dose 1 (N=X)			Day 9-29[a] Post Dose 1 (N=X)			Day 29[b]-36 Post Dose 2 (N=X)			Day 37-57 Post Dose 2 (N=X)			Day 180-187 Post Dose 3 (N=X)			Day 188-208 Post Dose 3 (N=X)			Day 209-360 Post Dose 3 (N=X)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**
Any SOC	Any PT	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any PT																					
	[PT 1]																					
	[PT 2]																					
[SOC 2]	Any PT																					
	[PT 1]																					
	[PT 2]																					

Note: N = Number of subjects in the Safety Population. This table presents number and percentage of subjects. For each time point, a subject is only counted once per PT.
a Day 29 prior to receiving Dose 2
b Day 29 after receiving Dose 2

Tables with similar format:

Table 43: Related Unsolicited Adverse Events Post Dosing by MedDRA System Organ Class and Preferred Term, Dose, and Treatment Group - Placebo

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 44: Listing of Serious Adverse Events

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , AE Number:												
Comments:												
Subject ID: , Treatment Group: , AE Number:												
Comments:												

Table 45: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , AE Number:										
Comments:										
Subject ID: , Treatment Group: , AE Number:										
Comments:										

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(not included in SAP, but this is a placeholder for the CSR)

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 46: Listing of Abnormal Laboratory Results - Chemistry

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

Table 47: Listing of Abnormal Laboratory Results - Hematology

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 48: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Chemistry Parameter

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 8	HEV-239											
	Placebo											
Day 36	HEV-239											
	Placebo											
Day 187	HEV-239											
	Placebo											
Max Severity Post Baseline	HEV-239											
	Placebo											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety Population

Table 49: Laboratory Results by Parameter Time Point, and Treatment Group – Creatinine

Time Point	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 8	HEV-239											
	Placebo											
Day 36	HEV-239											
	Placebo											
Day 187	HEV-239											
	Placebo											
Max Severity Post Baseline	HEV-239											
	Placebo											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety Population

Tables with similar format:

Table 50: Laboratory Results by Parameter Time Point, and Treatment Group – ALT

Table 51: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Chemistry Parameter

Time Point	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%
Day 8	HEV-239	x	x	xx	x	xx	x	xx
	Placebo							
Day 36	HEV-239							
	Placebo							
Day 187	HEV-239							
	Placebo							
Max Severity Post Baseline	HEV-239							
	Placebo							

Note: The "Max Post Baseline" rows indicate the maximum severity of abnormal laboratory results related to study treatment experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety Population

Table 52: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Creatinine

Time Point	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%
Day 8	HEV-239	x	x	xx	x	xx	x	xx
	Placebo							
Day 36	HEV-239							
	Placebo							
Day 187	HEV-239							
	Placebo							
Max Severity Post Baseline	HEV-239							
	Placebo							

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety Population

Tables with similar format:

Table 53: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – ALT

Table 54: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Creatinine

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	HEV-239	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Placebo					
Day 8	HEV-239					
	Placebo					
Day 8, Change from Baseline	HEV-239					
	Placebo					
Day 36	HEV-239					
	Placebo					
Day 36, Change from Baseline	HEV-239					
	Placebo					
Day 187	HEV-239					
	Placebo					
Day 187, Change from Baseline	HEV-239					
	Placebo					

Note: N=Number of subjects in the Safety Population

Tables with similar format:

Table 55: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – ALT

14.3.5.2 Hematology Results

Table 56: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Hematology Parameter

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 8	HEV-239											
	Placebo											
Day 36	HEV-239											
	Placebo											
Day 187	HEV-239											
	Placebo											
Max Severity Post Baseline	HEV-239											
	Placebo											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N =Number of subjects in the Safety Population

Table 57: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Hemoglobin

Time Point	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 8	HEV-239											
	Placebo											
Day 36	HEV-239											
	Placebo											
Day 187	HEV-239											
	Placebo											
Max Severity Post Baseline	HEV-239											
	Placebo											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N =Number of subjects in the Safety Population

Table 58: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – WBC

Time Point	Treatment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo																	
Day 8	HEV-239																	
	Placebo																	
Day 36	HEV-239																	
	Placebo																	
Day 187	HEV-239																	
	Placebo																	
Max Severity Post Baseline	HEV-239																	
	Placebo																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N =Number of subjects in the Safety Population

Table 59: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Absolute Neutrophil Count

Time Point	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 8	HEV-239											
	Placebo											
Day 36	HEV-239											
	Placebo											
Day 187	HEV-239											
	Placebo											
Max Severity Post Baseline	HEV-239											
	Placebo											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N =Number of subjects in the Safety Population

Tables with similar format:

Table 60: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Absolute Eosinophil Count

Table 61: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Platelets

Table 62: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Hematology Parameter

Time Point	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%
Day 8	HEV-239	x	x	xx	x	xx	x	xx
	Placebo							
Day 36	HEV-239							
	Placebo							
Day 187	HEV-239							
	Placebo							
Max Severity Post Baseline	HEV-239							
	Placebo							

Note: The "Max Post Baseline" rows indicate the maximum severity of abnormal laboratory results related to study treatment experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

Table 63: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group –Hemoglobin

Time Point	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%
Day 8	HEV-239	x	x	xx	x	xx	x	xx
	Placebo							
Day 36	HEV-239							
	Placebo							
Day 187	HEV-239							
	Placebo							
Max Severity Post Baseline	HEV-239							
	Placebo							

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

Table 64: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group –WBC

Time Point	Treatment Group	N	Mild/Grade 1 (Low)		Mild/Grade 1 (High)		Moderate/Grade 2 (Low)		Moderate/Grade (High)		Severe/Grade 3 (Low)		Severe/Grade 3 (High)	
			n	%	n	%	n	%	n	%	n	%	n	%
Day 8	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo													
Day 36	HEV-239													
	Placebo													
Day 187	HEV-239													
	Placebo													
Max Severity Post Baseline	HEV-239													
	Placebo													

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

Table 65: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group –Absolute Neutrophil Count

Time Point	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%
Day 8	HEV-239	x	x	xx	x	xx	x	xx
	Placebo							
Day 36	HEV-239							
	Placebo							
Day 187	HEV-239							
	Placebo							
Max Severity Post Baseline	HEV-239							
	Placebo							

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

Tables with similar format:

Table 66: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Absolute Eosinophil Count

Table 67: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group –Platelets

Table 68: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hemoglobin

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	HEV-239	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Placebo					
Day 8	HEV-239					
	Placebo					
Day 8, Change from Baseline	HEV-239					
	Placebo					
Day 36	HEV-239					
	Placebo					
Day 36, Change from Baseline	HEV-239					
	Placebo					
Day 187	HEV-239					
	Placebo					
Day 187, Change from Baseline	HEV-239					
	Placebo					

Note: N = Number of subjects in the Safety Population

Tables with similar format:

Table 69: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – WBC

Table 70: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Absolute Neutrophil Count

Table 71: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Absolute Eosinophil Count

Table 72: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Platelets

14.3.6 Displays of Vital Signs

Table 73: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Any Assessment

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 1 (Dose 1)	HEV-239											
	Placebo											
Day 8	HEV-239											
	Placebo											
Day 15	HEV-239											
	Placebo											
Day 29 (Dose 2)	HEV-239											
	Placebo											
Day 36	HEV-239											
	Placebo											
Day 43	HEV-239											
	Placebo											
Day 180 (Dose 3)	HEV-239											
	Placebo											
Day 187	HEV-239											
	Placebo											
Day 194	HEV-239											
	Placebo											
Max Severity Post Baseline	HEV-239											
	Placebo											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

Table 74: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Oral Temperature

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 1 (Dose 1)	HEV-239											
	Placebo											
Day 8	HEV-239											
	Placebo											
Day 15	HEV-239											
	Placebo											
Day 29 (Dose 2)	HEV-239											
	Placebo											
Day 36	HEV-239											
	Placebo											
Day 43	HEV-239											
	Placebo											
Day 180 (Dose 3)	HEV-239											
	Placebo											
Day 187	HEV-239											
	Placebo											
Day 194	HEV-239											
	Placebo											
Max Severity Post Baseline	HEV-239											
	Placebo											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

Table 75: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group –Pulse

Time Point	Treatment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	HEV-239	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo																	
Day 1 (Dose 1)	HEV-239																	
	Placebo																	
Day 8	HEV-239																	
	Placebo																	
Day 15	HEV-239																	
	Placebo																	
Day 29 (Dose 2)	HEV-239																	
	Placebo																	
Day 36	HEV-239																	
	Placebo																	
Day 43	HEV-239																	
	Placebo																	
Day 180 (Dose 3)	HEV-239																	
	Placebo																	
Day 187	HEV-239																	
	Placebo																	
Day 194	HEV-239																	
	Placebo																	
Max Severity Post Baseline	HEV-239																	
	Placebo																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population

Tables with similar format:

Table 76: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Systolic Blood Pressure

Table 77: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Diastolic Blood Pressure

14.4 Summary of Concomitant Medications

Table 78: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	HEV-239 (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
[ATC Level 1 – 2]	[ATC 1 - 2]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						

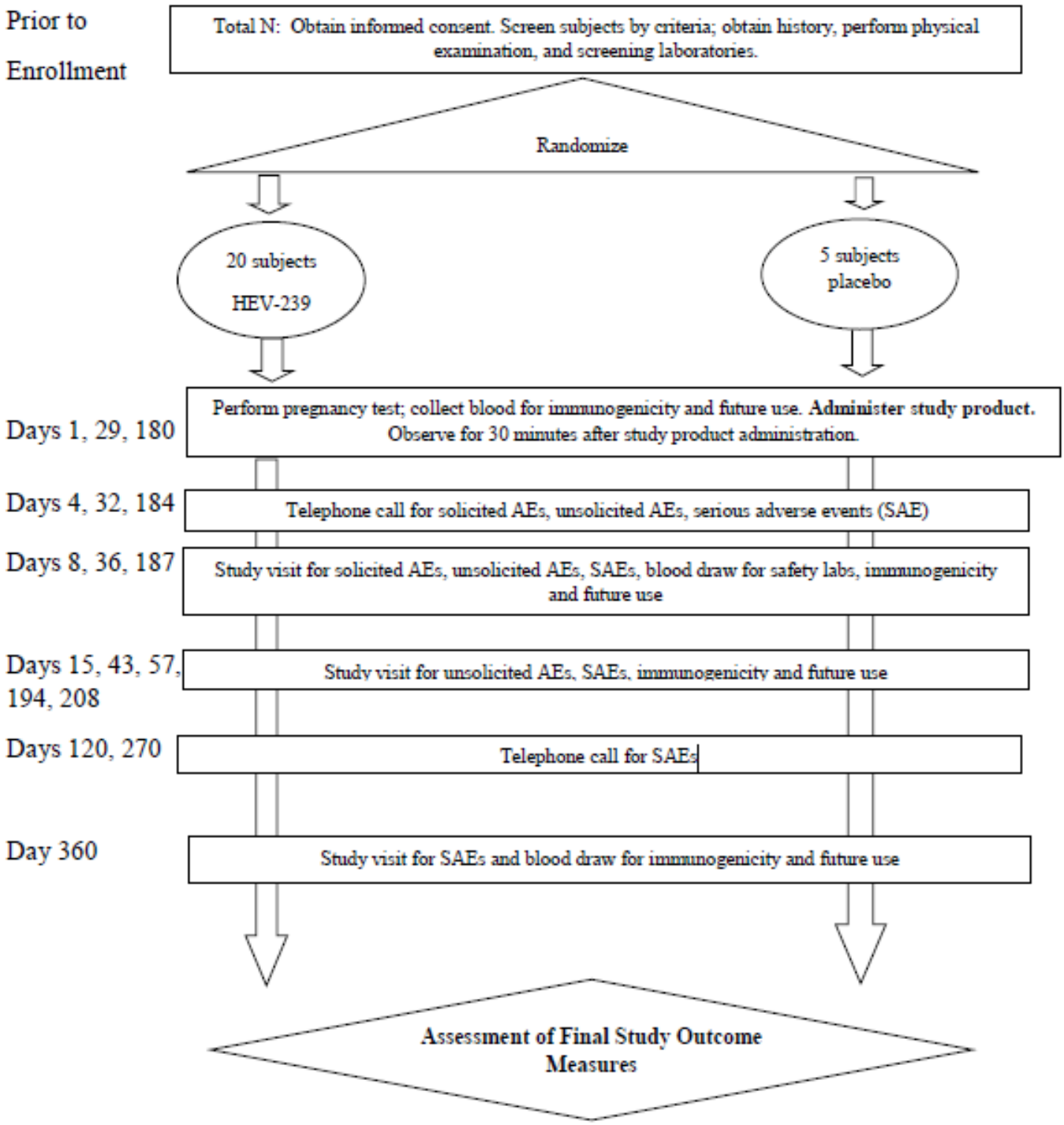
N = Number of subjects in the Safety Population n=Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

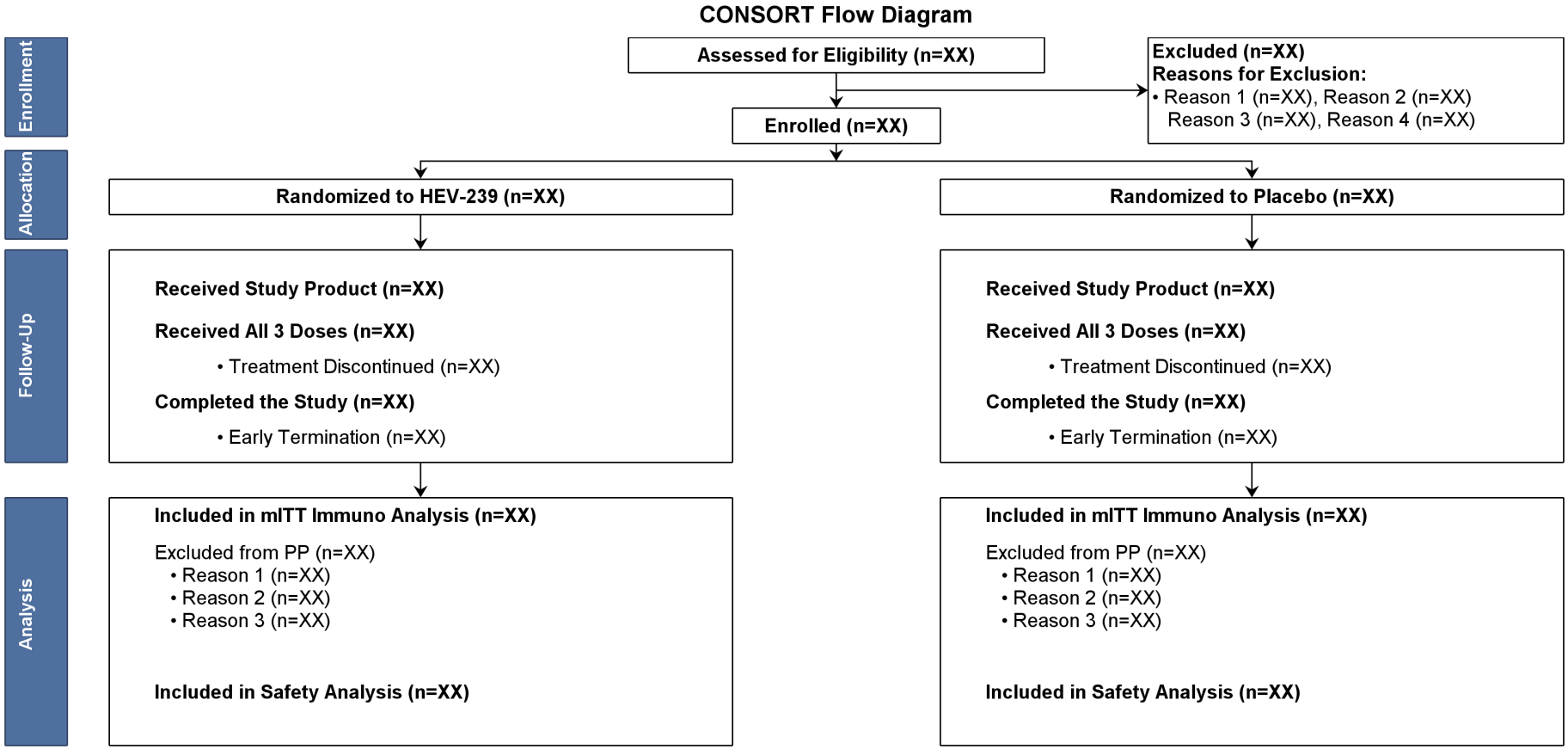
9.1 Overall Study Design and Plan Description

Figure 1: Study Design



10.1 Disposition of Subjects

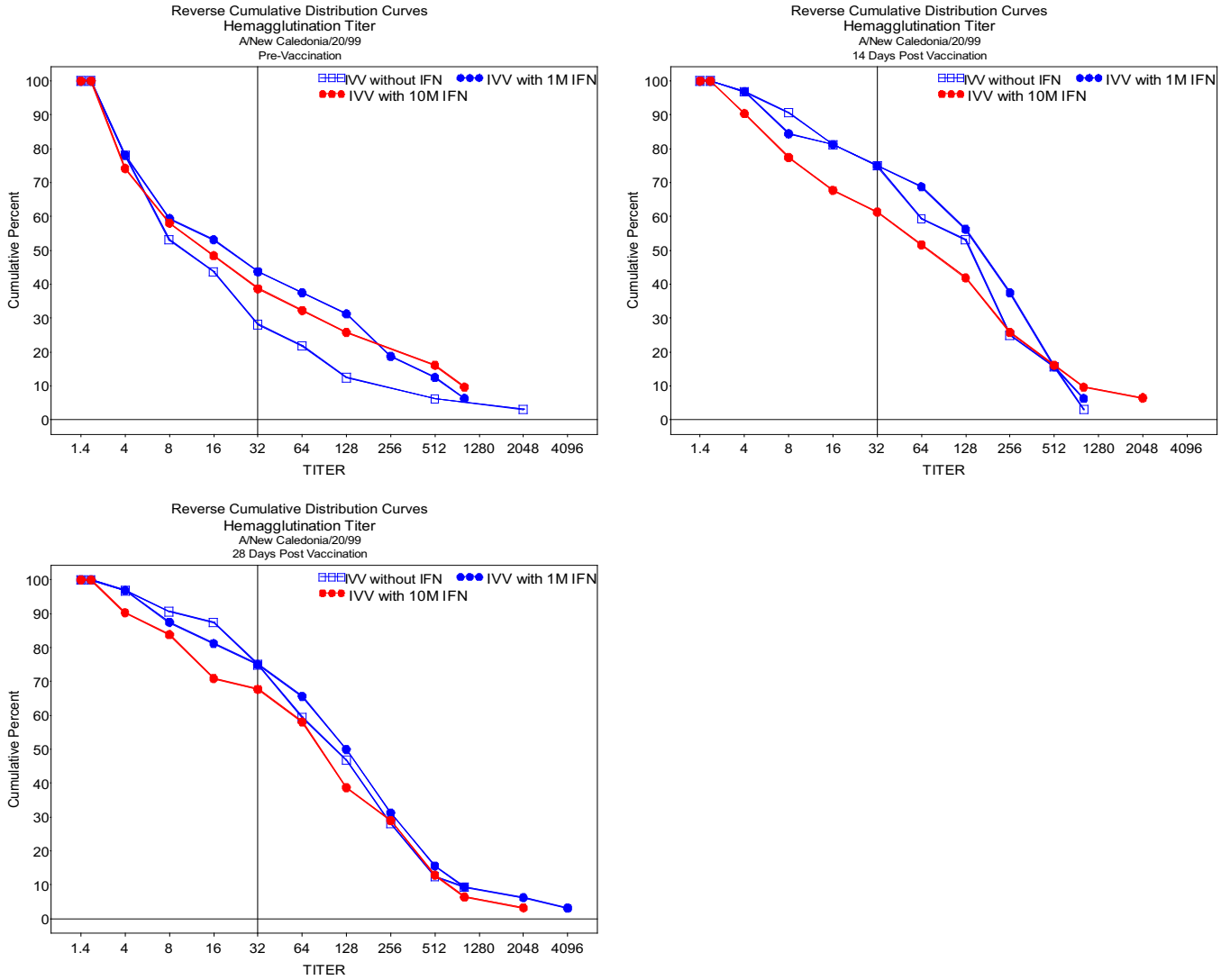
Figure 2: CONSORT Flow Diagram



14.2.2 Efficacy/Immunogenicity Response Figures by Measure, Treatment/Vaccination, and Time Point

Figure 3: Reverse Cumulative Distribution of Serum HEV IgG by Time Point and Treatment Group – mITT Population

[Implementation note: The figure below is an example only. Groups presented will be HEV-239 and Placebo and the figure will include 12 panels for Study Day 1, 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360.]



Figures with similar format:

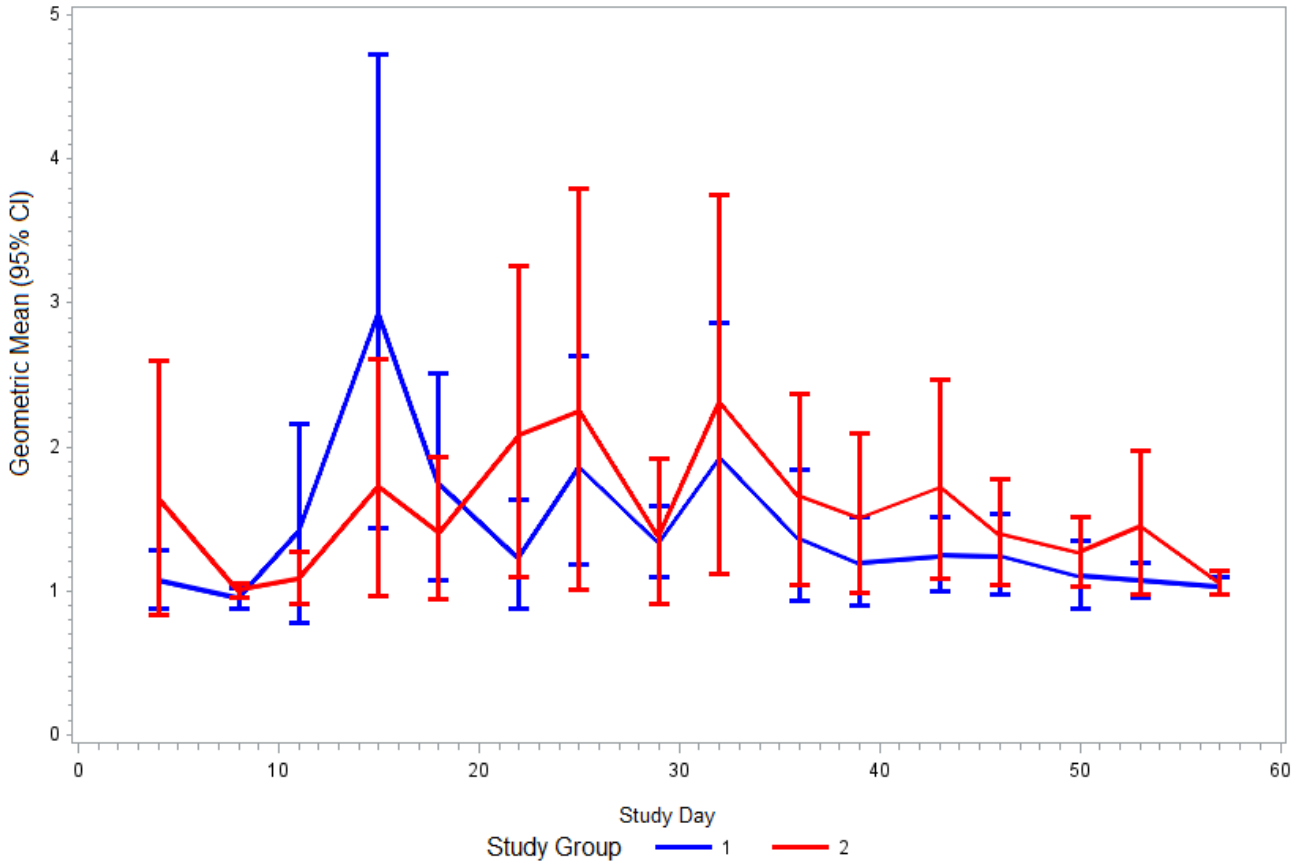
Figure 4: Reverse Cumulative Distribution of Serum HEV IgG by Time Point and Treatment Group – Per Protocol Population

Figure 5: Reverse Cumulative Distribution of Serum HEV IgM by Time Point and Treatment Group – mITT Population

Figure 6: Reverse Cumulative Distribution of Serum HEV IgM by Time Point and Treatment Group – Per Protocol Population

Figure 7: Geometric Mean Concentration of HEV IgG by Time Point and Treatment Group – mITT Population

[Implementation Note: The figure below is an example only. Groups presented will be HEV-239 and Placebo at Study Day 1, 8, 15, 29, 36, 43, 57, 180, 187, 194, 208, and 360. The y-axis will be labeled "Geometric Mean Concentration (95% CI)".]



Figures with similar format:

Figure 8: Geometric Mean Concentration of HEV IgG by Time Point and Treatment Group – Per Protocol Population

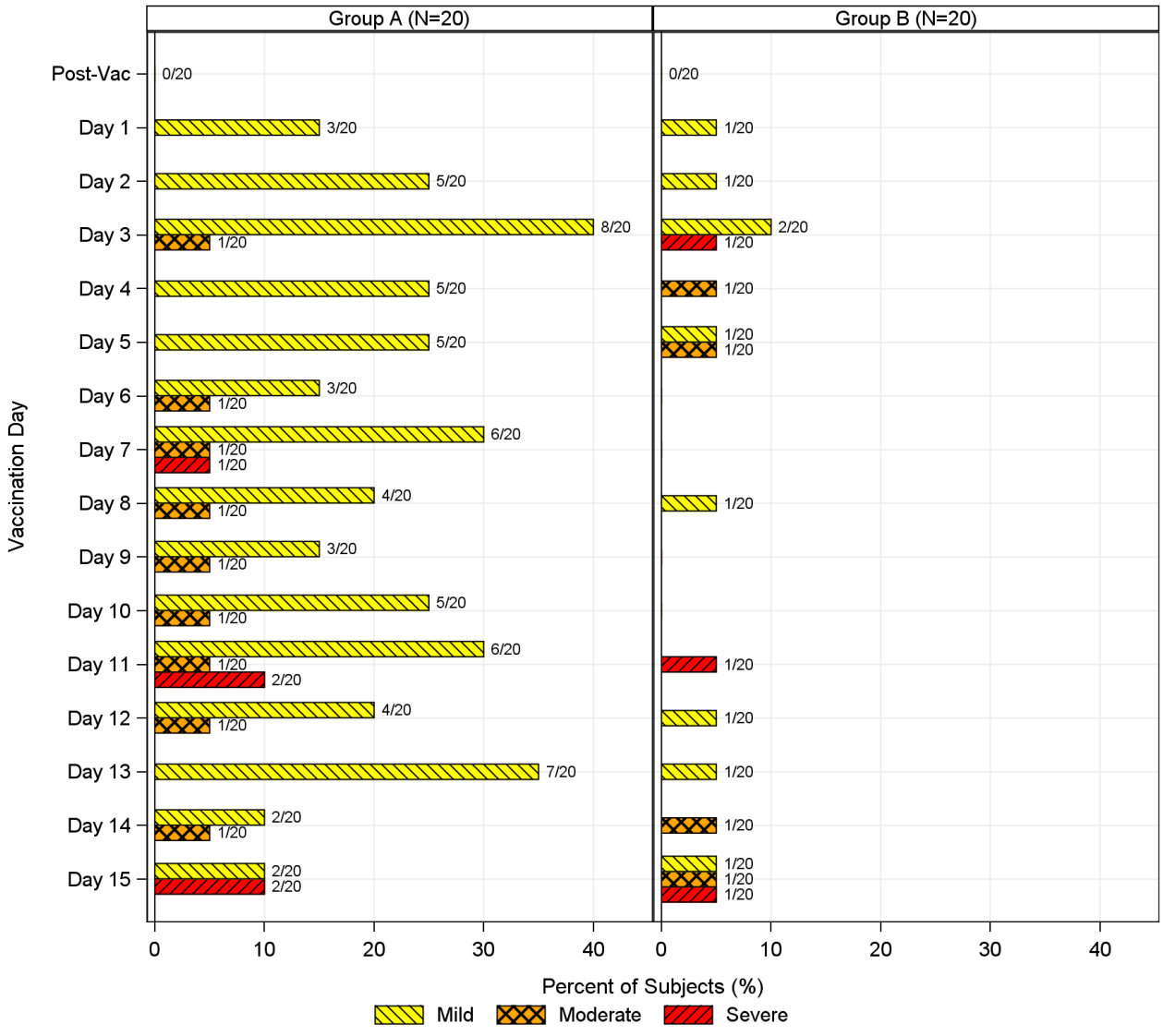
Figure 9: Geometric Mean Concentration of Serum HEV IgM by Time Point and Treatment Group – mITT Population

Figure 10: Geometric Mean Concentration of Serum HEV IgM by Time Point and Treatment Group – Per Protocol Population

14.3.1.1 Solicited Adverse Events

Figure 11: Maximum Severity of Solicited Systemic Symptoms per Subject by Day Post Treatment - Dose 1

[Implementation Note: The figure below is an example only. Groups presented will be HEV-239 and Placebo at Post-Dose Days 1 through 8.]



Figures with similar format:

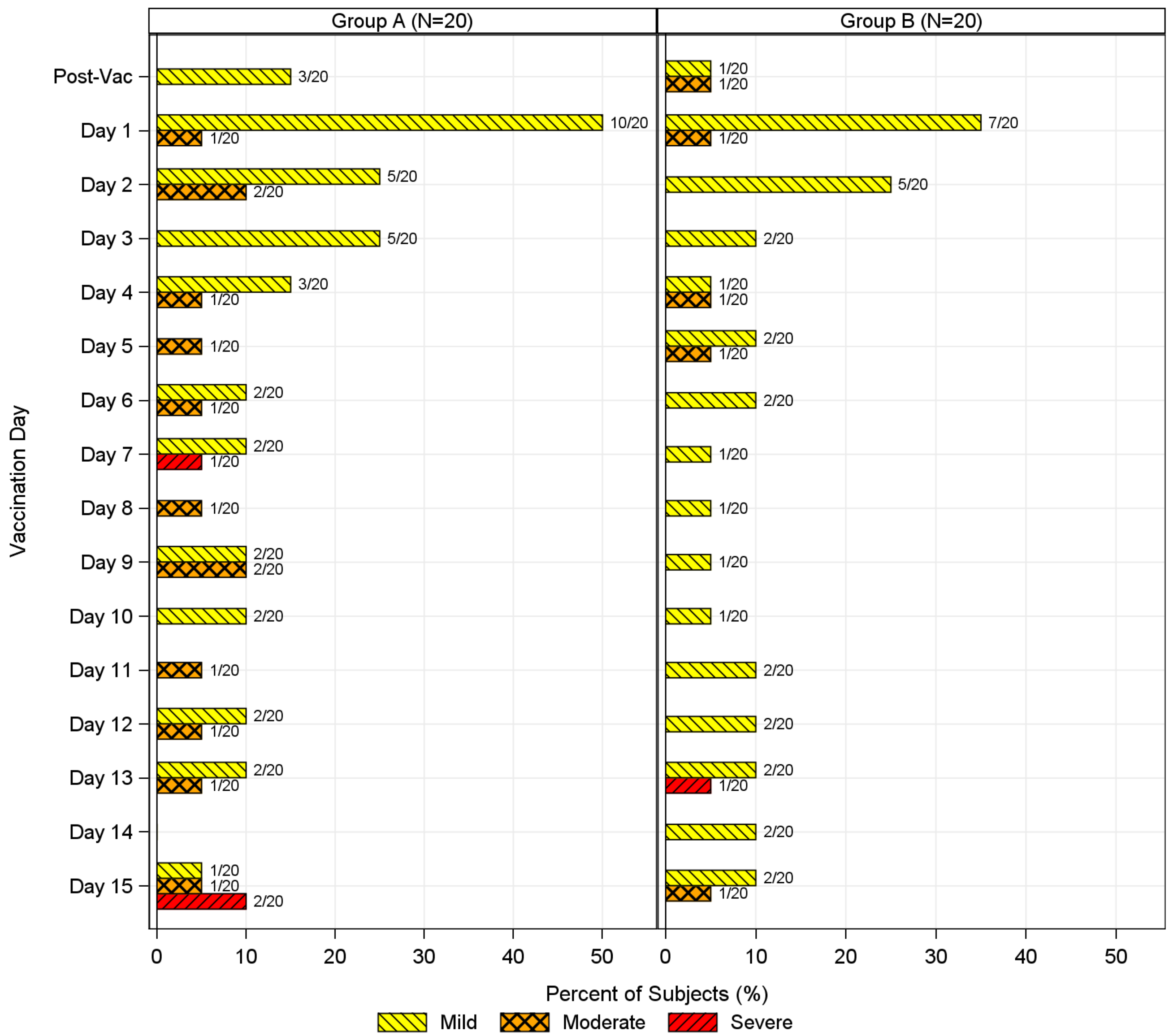
Figure 12: Maximum Severity of Solicited Systemic Symptoms per Subject by Day Post Treatment - Dose 2

Figure 13: Maximum Severity of Solicited Systemic Symptoms per Subject by Day Post Treatment - Dose 3

Figure 14: Maximum Severity of Solicited Systemic Symptoms per Subject by Day Post Treatment - Any Dose

Figure 15: Maximum Severity of Solicited Local Symptoms per Subject by Day Post Treatment – Dose 1

[Implementation Note: The figure below is an example only. Groups presented will be HEV-239 and Placebo at Post-Dose Days 1 through 8.]



Figures with similar format:

Figure 16: Maximum Severity of Local Systemic Symptoms per Subject by Day Post Treatment - Dose 2

Figure 17: Maximum Severity of Local Systemic Symptoms per Subject by Day Post Treatment - Dose 3

Figure 18: Maximum Severity of Local Systemic Symptoms per Subject by Day Post Treatment - Any Dose

14.3.1.2 Unsolicited Adverse Events

Figure 19: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity

[Implementation Note: The figure below is an example only. Groups presented will be HEV-239 and Placebo. This figure will include serious and non-serious unsolicited adverse events deemed related to study product. The SOCs will be sorted in descending frequency.]

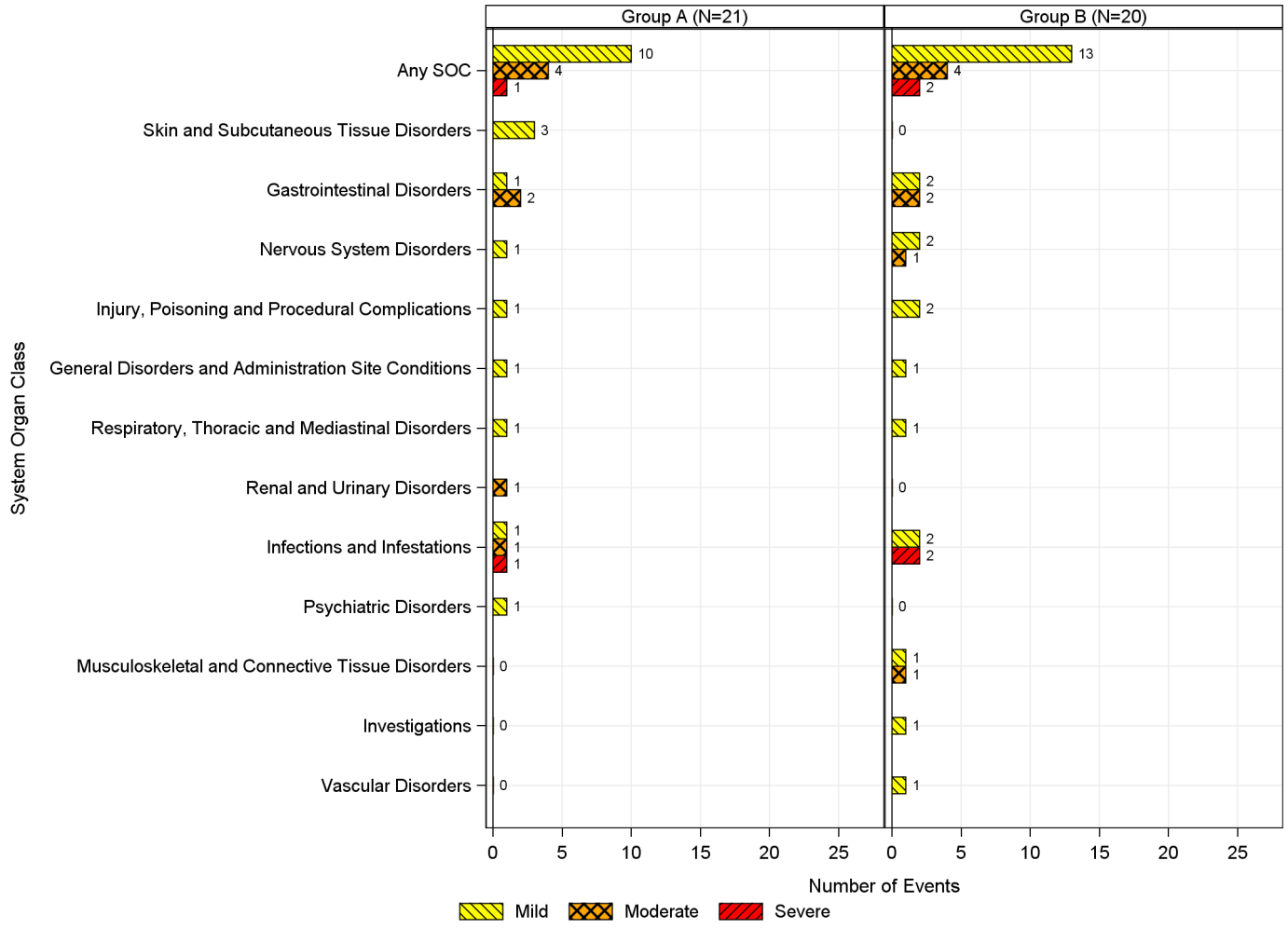
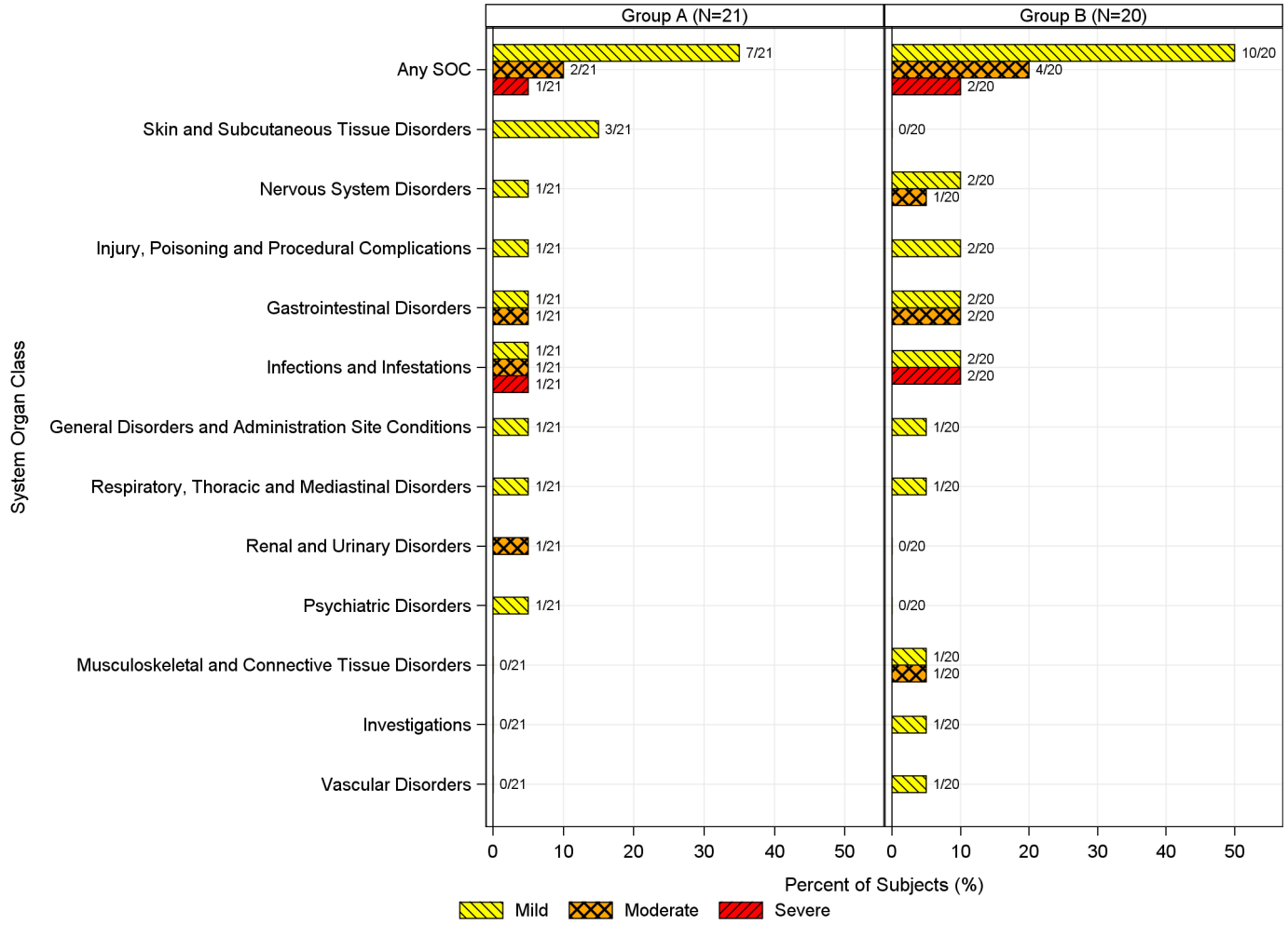


Figure 20: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity

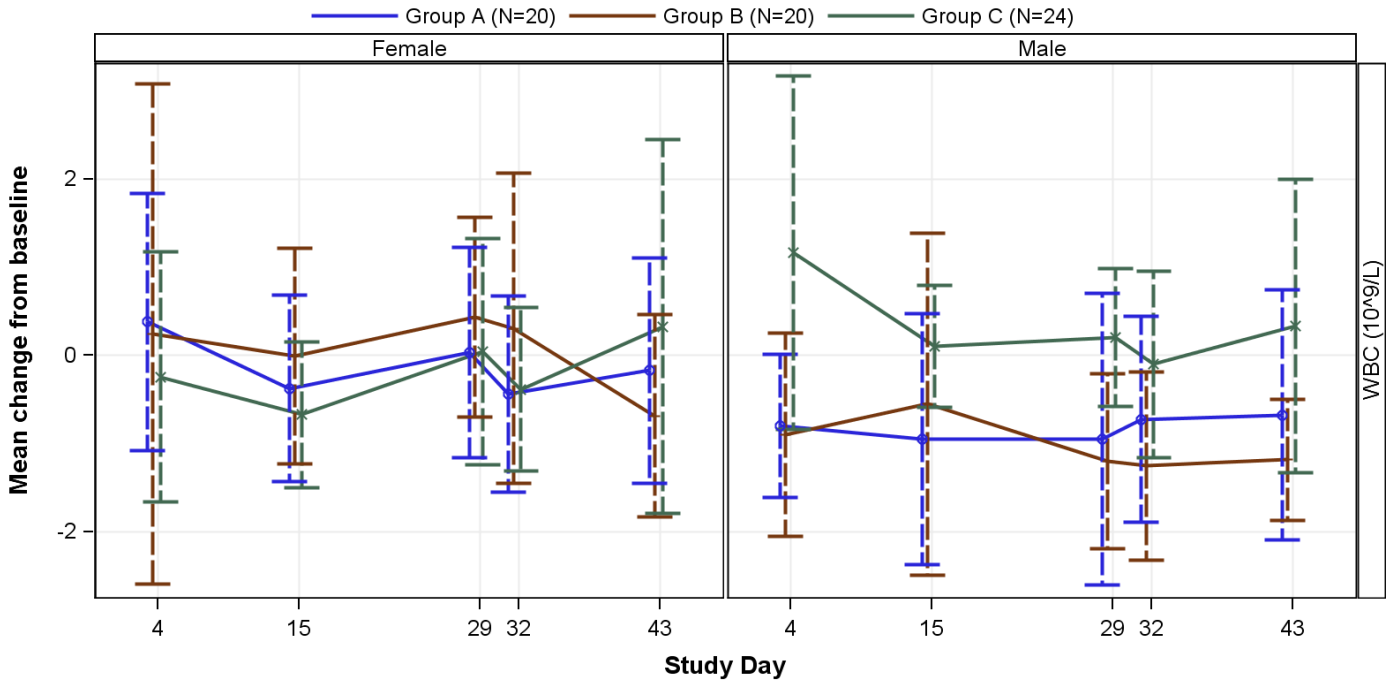
[Implementation Note: The figure below is an example only. Groups presented will be HEV-239 and Placebo. This figure will include serious and non-serious unsolicited adverse events deemed related to study product. The SOCs will be sorted in descending incidence.]



14.3.5 Displays of Laboratory Results

Figure 21: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Treatment Group –Creatinine

[Implementation note: The figure below is an example only. DMID 15-0108 graphs will present two treatment groups (HEV-239 and Placebo) at Study Day 8, 36, 180, and 187. Figures 24, 25, 26, and 27 will be a single panel rather than stratified by sex.]



Figures with similar format:

Figure 22: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Treatment Group –ALT

Figure 23: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, Sex, and Treatment Group –Hemoglobin

Figure 24: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Treatment Group –WBC

Figure 25: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Treatment Group –Absolute Neutrophil Count

Figure 26: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Treatment Group –Absolute Eosinophil Count

Figure 27: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Laboratory Parameter, and Treatment Group –Platelets

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

16.1.6 Listing of Subjects Receiving Investigational Product

(not included in SAP, but this is a placeholder for the CSR)

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 1: 16.2.1 Early Terminations or Discontinued Subjects

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 2: 16.2.2.1: Subject-Specific Protocol Deviations

Treatment Group	Subject ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

Listing 3: 16.2.2.2: Non-Subject-Specific Protocol Deviations

Site	Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 4: 16.2.3: Subjects Excluded from Analysis Populations

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., Safety, mITT, PP]	[e.g., Safety, mITT, PP, Day x]		

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

16.2.4 Demographic Data

Listing 5: 16.2.4.1: Demographic Data

Treatment Group	Subject ID	Sex	Age at Enrollment (years)	Ethnicity	Race

Listing 6: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

16.2.5 Compliance and/or Drug Concentration Data (if available)

Not applicable.

16.2.6 Individual Efficacy/Immunogenicity Response Data

Listing 7: 16.2.6: Individual Serum Antibody Concentration Data

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	HEV			
				IgG	IgG Fold-Rise	IgM	IgM Fold-Rise

16.2.7 Adverse Events

Listing 8: 16.2.7.1: Solicited Events – Systemic Symptoms

Treatment Group	Subject ID	Dose Number	Post Dose Day	Assessment[a]	Symptom	Severity	Attributed to Alternate Etiology?[b]	Alternate Etiology
				MA				
				Clinic				

[a] MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
[b] Grade 3 events only.
Note: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing 9: 16.2.7.2: Solicited Events – Local Symptoms

Treatment Group	Subject ID	Dose Number	Post Dose Day	Assessment[a]	Symptom	Severity
				MA		
				Clinic		

[a] MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
Note: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing 10: 16.2.7.3: Unsolicited Adverse Events

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	SAE?	Relationship to Study Treatment	In Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											

Note: For additional details about SAEs, see Table: 44

16.2.8 Individual Laboratory Measurements

Listing 11: 16.2.8.1: Clinical Laboratory Results – Chemistry

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

Listing 12: 16.2.8.2: Clinical Laboratory Results – Hematology

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

16.2.9 Vital Signs and Physical Exam Findings

Listing 13: 16.2.9.1: Vital Signs

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse (beats/min)	Weight (kg)	Height (cm)

Listing 14: 16.2.9.2: Physical Exam Findings

Treatment Group	Subject ID	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.10 Concomitant Medications

Listing 15: 16.2.10: Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)

16.2.11 Pregnancy Reports

Listing 16: 16.2.11.1: Pregnancy Reports – Maternal Information

Treatment Group	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?

Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.

Listing 17: 16.2.11.2: Pregnancy Reports – Gravida and Para

			Live Births												
Subject ID	Pregnancy Number	Gravida	Extremely PB[a] < 25 weeks	Very Early PB[a] 25-31 weeks	Early PB[a] 32-33 weeks	Late PB[a] 34-36 weeks	Early TB[b] 37-38 weeks	Full TB[b] 39-40 weeks	Late TB[b] 41 weeks	Post TB[b] ≥42 weeks	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?

Note: Gravida includes the current pregnancy, para events do not.
[a] Preterm Birth
[b] Term Birth

Listing 18: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?

Note: Congenital Anomalies are included in the Adverse Event listing.

Listing 19: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 20: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion