CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN

for

DMID Protocol: 17-0102

Study Title:

Phase I Study to Determine the Optimal Human Challenge Dose for Norovirus GII.4 CIN-3 Batch No.: 01-16C3

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Version 1.0

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RESTRICTED

PHASE I STUDY TO DETERMINE THE OPTIMAL HUMAN CHALLENGE DOSE FOR NOROVIRUS GII.4 CIN-3 BATCH NO.: 01-16C3

Protocol Number Code:	**DMID Protocol: 17-0102**
Development Phase:	Phase 1
Products:	GII.4 norovirus challenge
Form/Route:	Oral
Indication Studied:	Gastroenteritis Norovirus
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	March 28, 2022
Clinical Trial Completion Date:	Ongoing
Date of the Analysis Plan:	January 31, 2023
Version Number:	Version 1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALS	Antibody Lymphocyte Supernatant
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
ASC	Antibody Secreting Cell
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
C	Celsius
CBC	Complete Blood Count
CCHMC	Cincinnati Children's Hospital Medical Center
CDC	Centers for Disease Control
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DCC	Data Coordinating Center
DMID	Division of Microbiology and Infectious Diseases
ELISA	Enzyme-linked Immunosorbent Assay
ER	Emergency Room
F	Fahrenheit
FDA	Food and Drug Administration
GII.4	Norovirus genogroup II, genotype 4
GEC	Genome equivalent copies
GI	Gastrointestinal
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
HBGA	Histo-blood group antigens
HEENT	Head, Eyes, Ears, Nose, and Throat
Hgb	Hemoglobin

List of Abbreviations *(continued)*

HID_{50}	Human infectious dose 50%
HIV	Human
ICH	International Conference on Harmonisation
IDES	Internet Data Entry System
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IND	Investigational New Drug
IQR	Interquartile range
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IV	Intravenous
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantitation
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalent
mg	Milligram
mITT	Modified Intention to Treat
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Affairs
N	Number (typically refers to participants)
NIH	National Institutes of Health
NOCMC	New-Onset Chronic Medical Condition
NoV	Norovirus
NV	Norwalk Virus
OTC	Over The Counter
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase chain reaction
PI	Principal Investigator

List of Abbreviations *(continued)*

PP	Per Protocol
PT	Preferred Term
qRT-PCR	Quantitative Reverse Transcriptase Polymerase Chain Reaction (also known as Real-time PCR)
RCD	Reverse Cumulative Distribution
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SL	Scientific Lead
SMC	Safety Monitoring Committee
SOC	System Organ Class
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantitation
USP	United States Pharmacopeia
VLP	Virus-like particle
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "Phase I Study to Determine the Optimal Human Challenge Dose for Norovirus GII.4 CIN-3 Batch No.: 01-16C3" (DMID Protocol 17-0102) 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 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 efficacy and safety outcomes, and (4) a list of proposed tables and figures. Within the table, figure, and listing mock-ups (Appendices Appendix 1,Appendix 2, andAppendix 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

Norovirus (NoV) is a family of single-stranded, positive-sense RNA (Ribonucleic Acid) viruses that are a leading cause of gastroenteritis worldwide as well as the leading cause of foodborne-associated diarrheal outbreaks in the United States. The Centers for Disease Control (CDC) estimates that on an annual basis NoV is associated with 267M cases globally and 21M cases in the United States with 71,000 U.S. hospitalizations. NoV is particularly problematic in the extremes of age. On a yearly basis, throughout the world, NoV causes over 200K deaths/year, especially in children less than 5 years of age and is a common cause of ER visits and hospitalization among children in the United States [1]. In the US, NoV is estimated to be the cause of death of approximately 800 people over 65 years of age per year. All age groups are susceptible to NoV-related disease. Part of the reason is the diversity of NoV. Three different genogroups (GI, GII, and GIV) are capable of infecting humans, with ≥25 genotypes, and many subgroups [2]. Recombination of related viruses and error-prone RNA replication have contributed to the wide diversity of NoV [2]. Outbreaks usually have high attack rates and have occurred in childcare centers, schools, restaurants, summer camps, hospitals, nursing homes, ships (both civilian and military) as well as deployed military troops. The minimal infectious dose may be as low as 100 virions, which may be passed in foods, beverages, by person-to-person contact, via aerosols from vomit, and in contaminated ground waters [3]. NoV disease occurs throughout the year, though major outbreaks tend to occur during winter months.

NoV are difficult to study because: 1) they are genetically, and antigenically highly diverse and multiple strains co-circulate in the same communities, making diagnosis and disease control extremely difficult; 2) the virus cannot be cultivated long term in cell culture; and 3) no small animal model exists for studying human NoV. Several animals have been tested as potential models, including macaques, chimpanzees, and gnotobiotic pigs. Although chimpanzees can be infected with human NoV, they do not become ill [4]. Therefore, humans represent the only complete disease model for studying human NoV.

As not everyone gets infected or ill when exposed, it has been determined that susceptibility to NoV is modulated in part by specific, genetically determined carbohydrates in the gut known as the Histo-blood Group Antigens (HBGAs) [5]. These carbohydrates are found on the surfaces of red blood cells and mucosal epithelia. These antigens are also found circulating as free oligosaccharides in milk, saliva, and blood. Approximately 80% of humans (termed secretors) have a functional fucosyl transferase-2 (Fut-2) gene that leads to expression of HBGAs to which many NoVs can adhere. The remainder of the population lack a functional Fut-2 gene and are referred to as “non-secretors”. Only secretor-positive individuals can be infected with Norwalk Virus (NV), a genogroup 1 virus, supporting the theory that the H type 1 antigens are the cellular receptors for NV. Other HBGAs can also function as receptors, and different norovirus genogroups exhibit unique patterns of HBGA binding [6]. Additionally, challenge studies with Snow Mountain virus (GII.2) and outbreak studies with other GII viruses have reported infections in secretor negative individuals, suggesting the use of receptors other than the secretor-associated HBGAs [7, 8].

The initial outbreak of norovirus in Norwalk, Ohio was a GI.1 [9]. This isolate has been stored at the NIH as well as Baylor College of Medicine (Houston, Texas). The isolate has been used in clinical trials and the dose needed for the human infectious dose 50% (HID_{50}) has been determined [10]. This isolate also has been used in a challenge model to evaluate a genogroup I virus-like particle (VLP) vaccine [11]. However, currently, most NoV infections are due to genogroup II viruses and there is thought to be little to no cross-protection between genogroups [2, 12]. Therefore, the GI.1 challenge data cannot be used for genogroup II vaccine development. As described above, GII.4 NoV have been used in challenge models but the lowest dose capable of inducing infection in 50% of the susceptible participants has not been determined. This information is critical to the testing of agents designed to prevent or treat NoV. Concerns are that using a dose of NoV in excess of what a participant typically would encounter in nature could result in inappropriate rejection of a

promising vaccine or therapeutic. To facilitate these studies, dose range studies for both infection and illness for new GII inoculums must be completed. Once the shape of the dose-response relationship has been characterized, the optimal sample size and most efficient challenge doses needed for future trials can be accurately determined, limiting the expense, doses utilized, and health risk of these trials. By determining the dose-response relationship, future vaccine and therapeutic studies can make most efficient use of valuable challenge strains (i.e., a critical dose-sparing efficiency). Furthermore, with well-characterized challenge strains, we can more accurately estimate the efficacy of the vaccine or therapeutic treatment with minimal error in the estimate of the predicted infection rate without the vaccine.

2.1. Purpose of the Analyses

This is a Phase I study intended to determine the optimal challenge dose of Norovirus GII.4 CIN-3 Batch No.: 01-16C3 norovirus. Study results will also add to the determination of the CIN-3 challenge safety profile. This study will help assess the smallest dose of CIN-3 that can be used in vaccine challenge studies with an expected illness rate of approximately 50% in unprotected adults.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary

Determine the optimal challenge dose of Norovirus GII.4 CIN-3 Batch No.: 01-16C3 norovirus to achieve illness in ≥50% of participants (illness is defined as norovirus infection determined by positive PCR and either a) ≥3 loose or liquid stools, in a 24-hour period, b) ≥300 gm of loose or liquid stool in a 24-hour period c) and/or any episode of vomiting, during the inpatient period.

3.1.2. Secondary

1. Evaluate the safety of the Norovirus GII.4 CIN-3 Batch No.: 01-16C3 challenge strain
2. Determine the rate of infection at different challenge doses by:
   - Detection of norovirus GII.4 in the stool using specific quantitative Reverse Transcriptase-Polymerase Chain Reaction (qRT-PCR)
   - Anti- norovirus GII.4 serum Immunoglobulin G (IgG) by Enzyme-linked Immunosorbent Assay (ELISA) (≥4-fold rise from baseline through Day 30)
3. Measure the severity of acute gastroenteritis
4. Determine the quantity and duration of virus shedding in stool by qRT-PCR

3.1.3. Exploratory

1. Determine norovirus GII.4 -specific antibody responses at baseline, Day 15 and Day 30
   - Serum IgA and IgG by ELISA
   - Serum Blocking Antibody by ELISA
2. Determine total and norovirus GII.4 -specific Memory B cell response by ELISpot assay
3. Determine the effect of baseline norovirus antibody levels (serum IgG, IgA, and blocking antibody) on becoming infected with norovirus.
4. Determine total and norovirus GII.4 -specific IgA- and IgG-Antibody Secreting Cells (ASCs) by ELISpot assay and Antibody Lymphocyte Supernatant (ALS) by ELISA

3.2. Endpoints

3.2.1. Primary

The occurrence of NoV-associated illness (vomiting, diarrhea, positive PCR) in secretor positive participants through Day 4 after challenge.

3.2.2. Secondary

1. The number of participants with **solicited** adverse events through Day 10.
2. The number of **unsolicited** serious adverse events reported through Day 180.
3. The number of **unsolicited** Grade 3 adverse events from challenge to Day 30.

4. The number of participants with infection through Day 30 as determined by:
   - Detection of norovirus GII.4 in stool by qRT-PCR at Days 2, 3, 4, 5, 6, 15, 30; or
   - ≥4-fold rise from baseline in GII.4-specific antibody titers in serum IgG by ELISA through Day 30
5. Peak genome equivalent copies/g of virus in stool as measured by qRT-PCR after challenge through Day 60.
6. Duration (number of days) of viral secretion as measured by qRT-PCR after challenge through Day 60.
7. Modified Vesikari score through Day 4.
8. Duration (hours) of vomiting and/or diarrhea through Day 5.

3.2.3. Exploratory

1. Number of participants with ≥4-fold rise from baseline in GII.4-specific antibody titers in serum (IgA, IgG, Blocking Antibody) by ELISA at Day 15 and Day 30.
2. Baseline NoV GII.4 serum IgG, IgA, and blocking antibody titers in participants with and without infection.
3. Norovirus GII.4-specific Memory B cells determined by ELISpot using cryopreserved PBMCs (Ratio of antigen specific spot forming cells / 10^6 PBMC) baseline, Days 30 and 60.
4. Norovirus GII.4-specific IgA and IgG ASC per total IgA- or IgG-secreting ASCs at baseline and at Days 6 and 15.
5. Norovirus GII.4-specific IgA and IgG ALS by ELISA baseline and at Days 6 and 15.

3.3. Study Definitions and Derived Variables

3.3.1. Study Definitions

1. Illness is defined as norovirus infection, determined by a positive PCR, and either a) ≥ 3 loose or liquid stools in a 24-hour period, b) ≥ 300 gm of loose or liquid stool in a 24-hour period, and/or c) any episode of vomiting.
2. Adverse Event (AE): ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
3. Any medical condition that is present at the time that the participant 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.
4. Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
   - death

- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization (excluding any extended stay during challenge admission due to continued vomiting, diarrhea, etc.)
- a persistent or significant incapacity of substantial disruption of the ability to conduct normal life functions
- 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 participant 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.

5. Life-threatening AE: An adverse event is considered "life-threatening" if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an adverse event, had it occurred in a more severe form, might have caused death.
6. New-Onset Chronic Medical Conditions (NOCMCs): NOCMCs are defined as any new ICD-10 diagnosis that is applied to the participant during the duration of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.

3.3.2. Derived Variables

The baseline value will be defined as the last value obtained prior to the administration of the challenge product.

Fold-rise will be calculated as the ratio of: post-challenge titer / pre-challenge titer.

For serum antibody results, the titer of a sample is the reciprocal of the last dilution of serum that gives a corrected optical density value >0.2. If the corrected optical density value at the lowest dilution of the serum is ≤0.2, then the titer is reported as one-half of the limit of detection (LLOD)/lower limit of quantitation (LLOQ). Values above the upper limit of quantitation (ULOQ) will be imputed as the ULOQ.

The ratio of GII.4-specific ASCs per total ASCs will be calculated separately for IgA and IgG for each participant and at each time point, by dividing the GII.4-specific ASCs over the total ASCs.

The following definitions and derivations will be used for illness and infection endpoints:

1. Diarrhea [Boolean variable]: Defined as Grade 1 or higher per the grading scale in Table 5 (3 or more loose or watery stools or > 300 gm of loose or watery stools in 24 hours). The 24-hour period is defined as a study day from 00:00 to 23:59.
2. Duration of diarrhea [hours]: The duration of diarrhea during the inpatient period will be calculated for participants who had at least three stools classified as having loose or watery consistency, or who have at least two stools classified as having loose or watery consistency with > 300 gm of loose or watery stools in a study day (from 00:00 to 23:59). The duration of diarrhea will be calculated as the interval between the first time a loose/watery stool is produced on a day the participant met the

criteria for diarrhea through the last loose/watery stool on a day the participant met the criteria for diarrhea. The number of hours calculated for each participant will be rounded to 2 decimal places. The inpatient period is considered the time until a participant is discharged, even if they are discharged before or after the planned discharge day.

3. Vomiting [Boolean variable]: Defined as Grade 1 or higher per the grading scale in Table 5 (at least one episode of vomiting in 24 hours, where a 24-hour period is defined as a study day from 00:00 to 23:59).
4. Duration of vomiting [hours]: The duration of vomiting during the inpatient period will be calculated similarly to the duration of diarrhea, however, it will be calculated for participants who had at least two episodes of vomiting in a study day or over two consecutive days. The number of hours calculated for each participant will be rounded to 2 decimal places. The inpatient period is considered the time until a participant is discharged, even if they are discharged before or after the planned discharge day.
5. Duration of diarrhea and vomiting [hours]: The duration of diarrhea and/or vomiting will be calculated using the same criteria as above beginning from the first diarrheal stool or episode of vomiting until the last diarrheal stool or episode of vomiting during the inpatient period.
6. Infection [Boolean variable]: Detection of norovirus in stool sample by real-time PCR, reported as a positive qualitative result.
7. Norovirus-associated illness [Boolean variable]: Diarrhea and/or vomiting during the inpatient period with infection.
8. Inpatient period [days]: The inpatient period is considered the time from challenge until a participant is discharged, even if they are discharged before or after the planned discharge day.
9. Peak virus in stool as measured by qRT-PCR [genome equivalent copies per gram of stool (GEC/g)]: The maximum GEC/g of all available stool samples tested post-challenge.
10. Duration of viral secretion as measured by qRT-PCR [days]: For participants with infection (per definition #6 above) on at least one day, duration will be based on the first and last days where norovirus is detected. A participant who only had norovirus detected on one day will have a duration of 1 day.
11. Modified Vesikari Score [Unitless score between 0 and 17]: The score is made up of the following components: duration of diarrhea (days), maximum number of diarrheal stools per 24 hours, duration of vomiting (days), maximum number of vomiting episodes per 24 hours, fever, and dehydration. For all components, the inpatient period is considered the time until a participant is discharged, even if they are discharged before or after the planned discharge day. Here, the duration of diarrhea and maximum number of diarrheal stools per study day will be calculated based on all stools which were labeled as loose or watery. Thus, participants who did not meet the definition of diarrhea as defined in #1, could have a diarrhea score of 1 or greater in the modified Vesikari scale. Duration of vomiting will be determined by the number of days during the participant's inpatient stay that they reported at least one episode of vomiting. For both diarrhea and vomiting durations, days do not have to be consecutive. For example, if a participant has 3 loose or watery stools on Day 1, no loose or watery stools on Day 2, and 3 loose or watery stools on Day 3, this participant would have "2" days entered as the duration. The maximum number of vomiting episodes per 24 hours will be determined by the maximum number of episodes reported per study day during the participant's inpatient stay. The maximum oral temperature obtained during the inpatient period will be converted to a rectal

temperature by adding 0.3°C and assigning a point value based on the modified Vesikari scale in Table 6. Dehydration will be determined by the presence or absence of IV rehydration treatment during the inpatient period, as reported on the concomitant medications form. Each of the components will be assigned a point value based on and the points will be summed to create a total score out of a possible 17 for each participant.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a double-blind, safety and infectivity study of experimental human Norovirus genogroup GII.4 administered to healthy non-pregnant adults, 18-49 years of age, inclusive.

Participants will be admitted to an inpatient unit and then challenged with a dose of human norovirus GII.4 challenge strain. Participants will be housed in the Vaccine Research Center inpatient facility and administered the dose according to cohort. The challenge study will be conducted in 3 cohorts of approximately 16 participants each, with the initial cohort receiving $3.5x10^3$ copies of norovirus. For every 16 participants, 15 will be chosen because they have a functional FUT-2 gene (secretor positive) and 1 will be chosen because they lack a nonfunctional FUT-2 gene (non-secretor). Every participant in a cohort will receive the same dose of norovirus. From previous studies we have conducted with this GII.4 norovirus, only 1 "non-secretor" became infected and the symptoms experienced were very mild. Thus, administration of a dose of a GII.4 norovirus to a non-secretor is in effect administering a placebo.

Based on the illness rate of participants meeting the primary outcome measure in secretor positive participants of the initial cohort, a series of decision rules will be implemented (Figure 1) with regards to dosing of the second cohort and third cohort.

Participants will remain in the inpatient facility for at least four days following challenge and assessed daily for clinical and virologic evidence of norovirus infection. Discharge criteria are listed in Protocol Section 6.1.3. Participants will return to the investigational site for evaluation on Day 6 (6-8 days), 15 (14-16 days,), 30 (28-35 days), 45 (40-45 days), and 60 (55-65 days) post challenge.

Approximately 180 days after receiving virus challenge, a final study contact will be performed to obtain an interim medical history. Adverse events limited to new-onset chronic medical conditions and SAEs that have occurred since the last visit will be solicited.

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

The challenge study will be conducted in three cohorts of approximately 16 participants each, with the initial cohort receiving 3.5x103 copies of norovirus. For every 16 participants, 15 will be chosen because they have a functional FUT-2 gene (secretor positive) and one will be chosen because they lack a functional FUT-2 gene (non-secretor). Every participant in a cohort will receive the same dose of norovirus. From previous studies conducted with this GII.4 norovirus, only one "non-secretor" became infected and the symptoms experienced were very mild. Thus, administration of a dose of a GII.4 norovirus to a non-secretor is in effect administering a placebo.

4.3. Selection of Study Population

The study is designed for the enrollment of healthy adults. The following eligibility criteria will be used.

Inclusion Criteria

Participants eligible to participate in this study must meet all of the following criteria:

1. Participant able to provide informed consent.
2. Male or non-pregnant females between the ages of 18 and 49 years, inclusive.

3. Women of childbearing potential must be using an acceptable method of birth control for at least 30 days prior to enrollment through day 45 after receipt of challenge virus.
    - A woman is considered of childbearing potential unless post-menopausal (absence of menses for >1 year) or surgically sterilized (tubal ligation, bilateral oophorectomy or hysterectomy).
    - Acceptable contraception methods for women include but are not limited to: sexual abstinence from intercourse with men, monogamous relationship with vasectomized partner who has been vasectomized for 6 months or more prior to the participant enrolling in the study, barrier methods such as condoms or diaphragms with spermicide or foam, effective devices (IUDs, NuvaRing®) or licensed hormonal products such as implants, injectables or oral contraceptives.
4. For women of childbearing potential, must have a negative serum or urine pregnancy test at screening.
5. Are in good general health.
6. Demonstrate knowledge and comprehension of the study by scoring ≥70% on a quiz (test of understanding) of the study protocol and policies.
7. Willing and able to participate in all study visits, including an inpatient stay of at least 96 hours.

Exclusion Criteria

Participants who meet any of the following exclusion criteria will be excluded from study participation:

1. Have household contact with or have daily contact with children less than 2 years of age or persons older than 70 years of age.
2. Have expected extended social contact (> 2 hours/day) with immunocompromised individuals in the 8 weeks after challenge, including persons with HIV infection or active cancer, children <2 years of age, pregnant women or persons who are immunosuppressed (e.g. history of stem cell or organ transplantation) and/or provide any child day care services (in-home or non-residential facility).
3. Are healthcare workers with direct patient contact or any child day care services (in-home or non-residential facility) in the 8 weeks after challenge.
4. Are positive for COVID-19 by an antigen test at the time of admission to the challenge unit.
5. Are food service workers expected to prepare/handle food in the 8 weeks after challenge.
6. Plan to be living in a confined communal environment (e.g. ship, camp, or dormitory) within 8 weeks after receiving the challenge strain.
7. For females, are pregnant or plan to become pregnant at any time between the Screening Visit through 45 days after receipt of the challenge virus.
8. Are breastfeeding or plan to breastfeed at any given time throughout the study.
9. Have a history of acute gastroenteritis in the 4 weeks prior to challenge or any history of chronic or recurrent diarrhea or vomiting.
10. History of significant GI condition including; malabsorption, major GI surgery, current eating disorder, irritable bowel syndrome, or any GI disorder (deemed clinically significant by study physician) making it unsafe to participate.
11. Have significant acute illness or an oral temperature >100.4°F within seven days prior to challenge.

12. Have a heart rate <45 beats per minute (bpm) or >100 bpm. If heart rate is <45 beats per minute and the investigator determines that this is not clinically significant (e.g., athletes) and heart rate increases >45 beats per minute on moderate exercise (two flights of stairs), participant will not be excluded. If a participant has significant abnormalities in their heart rate, they will be informed of the values and advised to seek care from their physician.
13. Systolic blood pressure less than 90 mm Hg or greater than 150 mm Hg on two separate measurements (screening and baseline prior to challenge). If a participant has significant abnormalities in their blood pressure, they will be informed of the values and advised to seek care from their physician.
14. Diastolic blood pressure less than 50 mm Hg or greater than 90 mmHg on two separate measurements (screening and baseline, prior to challenge).
15. Have long-term use (>2 weeks) of high-dose oral (>20 mg per day prednisone or equivalent) or parenteral glucocorticoids, or high-dose inhaled steroids for greater than 7 days in the last 6 months.
16. Have an autoimmune, inflammatory, vasculitic or rheumatic disease, including but not limited to systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis or scleroderma.
17. Have HIV, Hepatitis B, or Hepatitis C. Participants will be tested for HIV, Hepatitis B surface antigen, and antibody to Hepatitis C at screening only. Any participants having HIV, Hepatitis B, Hepatitis C infection will not be enrolled into the study.
18. Have a seizure disorder.
19. Have an active malignancy or history of malignancy (Excluding nonmelanotic skin cancer in remission without treatment for more than 5 years) or current use of immunosuppressive or cytotoxic therapy.
20. Have abnormal screening laboratory test results per laboratory reported normal values for white blood cells (WBCs), hemoglobin (Hgb), platelets, absolute neutrophil count (ANC), total bilirubin, potassium, sodium, and urine protein.
21. Serum creatinine greater than a Grade 1 adverse event on enrollment.
22. Alanine aminotransferase (ALT), greater than 1.0xULN.
23. Have a chronic condition that the study physician feels would pose a threat to participating participants. Including, but not limited to solid organ or stem cell transplantation, diabetes, clinically significant history of immunosuppressive illness, gall bladder disease, heart disease, lung disease, pancreatic disease, renal disease or neurological disease.
24. Have ongoing drug abuse/dependence (including alcohol), or a history of these issues within 5 years of enrollment.
25. Have a positive urine test for opiates.
26. Have any medical, psychiatric, occupational, or behavioral problems that make it unlikely for the participant to comply with the protocol as determined by the investigator.
27. Are unwilling to comply with study procedures including abstaining from smoking for the duration of the inpatient portion of the study.
28. Have participated in a previous NoV challenge study or NoV vaccine study.
29. Have received experimental products within 30 days before study entry or plan to receive experimental products at any time during the study.

30. Plans to enroll in another clinical trial that could interfere with safety assessment of the investigational product at any time during the study period, including study interventions such as drugs, biologics or devices.
31. Plan to donate blood during the course of the study.
32. Have received a live vaccine within 30 days before study entry or plan to receive a live vaccine prior to Day 30 of the study.
33. Have received, or plan to receive, an inactivated vaccine within 14 days of challenge to 14 days after challenge.
34. Received parenteral immunoglobulin or blood products within 3 months of challenge, or plan to receive parenteral immunoglobulin/blood products within 3 months after challenge.
35. Use of antibiotics within 7 days prior to entry into the inpatient facility.
36. Use of prescription and OTC medications containing acetaminophen, aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs within 48 hours prior to NoV challenge.
37. Regular use of laxatives or anti-motility agents.
38. Have a history of allergy to sodium bicarbonate.
39. Have had a recent norovirus infection or have ever had a norovirus vaccine.

4.4. Treatments

4.4.1. Treatments Administered

Cohorts of participants will be sequentially challenged with doses of human challenge stock of the Norovirus genogroup II, genotype GII.4 starting with $3.5x10^3$ copies of norovirus.

4.4.2. Identity of Investigational Product(s)

As part of the studies where the GII.4 strain was used in human challenges; samples of diarrhea were saved from all participants who developed diarrhea after receiving the challenge strain. These stool samples were aseptically transferred to storage containers and have been maintained at ≤ -60°C in a temperature monitored freezer for subsequent use. Due to exhausting the supply of the original GII.4 challenge pool; samples collected from a participant in previous challenge studies has been used to prepare a new challenge pool.

The GII.4 challenge to be used in this study was isolated in 2011 from a stool sample collected as part of an inpatient challenge model of norovirus (Participant 02CCI0249). The donor is a male who was 31 years old at the time of sample donation. He had no prior history of hospitalization or serious illness. To determine eligibility for enrollment into the challenge study, the sample donor was tested for anti- HAV IgM, HBsAg, anti-HCV as well as HIV, all of which were negative. He also had stool culture for routine enteric pathogens and stool ova and parasite examination, again, all of which was negative. Testing of his blood pre-challenge demonstrated a normal CBC and AST of 55 international units (IU) (normal range 30-65 IU). The stool donor received a dose of the previous challenge strain (CIN-1) on October 24, 2011. The following day, the donor began to develop diarrhea which lasted 2 days and then resolved spontaneously. During the 2-day illness, the participant had 10 diarrheal stools.

To make the challenge product to be used in the current study; 2 diarrheal stool samples were combined and the final product (Norovirus GII.4 CIN-3 Batch No.: 01-16C3) was prepared by executing a series of

processing steps, including dilution of the original donor specimen, centrifugation, filtration, and filling. Aliquots of the unfiltered stool sample (10% dilution of the 2 pooled diarrheal stool samples) was tested for rotavirus, enteric adenovirus, astrovirus, hepatitis A, HIV-1, HIV-2, cytomegalovirus, hepatitis B virus, and hepatitis C virus, as well as *in vitro* and *in vivo* adventitious viral contamination (*in vitro* AA (amino acid) and *in vivo* AA). Samples of the final product, Norovirus GII.4 Norovirus GII.4 CIN-3 Batch No.: 01-16C3, were tested for sterility, identity and potency by quantitative RT-PCR, direct and indirect methods for the detection of mycoplasma, as well as bacterial endotoxin.

The final challenge product Norovirus GII.4 CIN-3 Batch No.: 01-16C3 was aliquoted into sterile 2mL centrifuge tubes with fill volumes of 1-1.5mL at a concentration of approximately 3.5x105 copies/mL. The challenge material is clear to amber in color and is being stored at ≤ -60°C in a temperature monitored freezer.

Norovirus GII.4 CIN-3 Batch No.: 01-16C3
The filled, purified study product is formulated in sterile water for injection, USP in 2mL sterile cryovials, in volumes of 1-1.5mL at a concentration of 3.5x105copies/mL. The study product will be labeled according to manufacturer or regulatory specifications and include the statement "Caution: New Drug – Limited by Federal Law to Investigational Use"

Diluent - Sterile Water for Injection, USP
The sterile water for injection, USP is non-pyrogenic and contains no bacteriostatic, antimicrobial agent, or added buffer. This product will be used to dilute the Norovirus GII.4 CIN-3 Batch No.: 01-16C3 and will be supplied as a 2 mL single-dose cryovial. A label with the statement "Caution: New drug -Limited by Federal Law to Investigational Use" will be placed on the immediate package.

Buffer - Sodium Bicarbonate, USP
The Sodium Bicarbonate, USP is a white, odorless, crystalline powder. This product will be used to prepare the buffer. A label with the statement "Caution: New drug -Limited by Federal Law to Investigational Use" will be placed on the immediate package.

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

This is a non-randomized dose escalation study in which all participants in a cohort will receive the same dose of challenge product. Enrollment will be done online using the enrollment module of the Data Coordinating Center's (DCC) Internet Data Entry System (IDES).

4.4.4. Selection of Doses in the Study

Cohort 1 will be challenged with a dose of $3.5x10^3$ copies of CIN-3 norovirus. This dose was chosen as the starting dose because from a previous GII.4 NoV challenge study at CCHMC, approximately the same dose resulted in a 70% rate of infection and 50% rate of disease. If less than 50% of participants become ill, Cohort 2 will receive a dose of $3.5x10^4$ copies. If 50% or more of participants in Cohort 1 become ill, Cohort 2 will receive a dose of $3.5x10^2$ copies.

If Cohort 2 receives a dose of $3.5x10^4$ copies of CIN-3 norovirus, and less than 50% of participants become ill, Cohort 3 will receive a dose of $3.5x10^5$ copies. If 50% or more of participants in Cohort 2 who receive a $3.5x10^4$ dose become ill, then Cohort 3 will receive a dose of $1.75x10^4$ copies.

If Cohort 2 receives a dose of $3.5x10^2$ copies of CIN-3 norovirus, and less than 50% of participants become ill, cohort 3 will receive a dose of $1.75x10^3$ copies. If 50% or more of participants in Cohort 2 who receive a $3.5x10^2$ dose become ill, then Cohort 3 will receive a dose of $3.5x10^1$ copies.

If Cohort 3 receives a dose of $3.5x10^5$ copies of CIN-3 norovirus, and 50% or more of participants become ill, the final dose selection for future study will be $1.75x10^5$ copies.

If Cohort 3 receives a dose of $1.75x10^4$ copies of CIN-3 norovirus, and less than 50% of participants become ill, the final dose selection for future study will be $3.5x10^4$ copies. If 50% or more of participants in Cohort 3 who receive a $1.75x10^4$ dose become ill, then the final dose selection for future study will be $7x10^3$ copies.

If Cohort 3 receives a dose of $1.75x10^3$ copies of CIN-3 norovirus, and less than 50% of participants become ill the final dose selection for future study will be $3.5x10^3$ copies. If 50% or more of participants in Cohort 3 who received a $1.75x10^3$ dose become ill, then the final dose selection for future study will be $7x10^2$ copies.

If Cohort 3 receives a dose of $3.5x10^1$ copies of CIN-3 norovirus, and less than 50% of participants become ill the final dose selection for future study will be $1.75x10^2$ copies. If 50% or more of participants in Cohort 3 who receive a $3.5x10^1$ dose become ill, then the final dose selection for future study will be $1.75x10^1$ copies.

4.4.5. Selection and Timing of Dose for Each Participant

Participants will receive a single oral dose of CIN-3 inoculum on Day 1 of their inpatient stay at the clinical site. The dose will be determined as specified above.

On the day of Norovirus challenge, the study product will be removed from the freezer and thawed on wet ice for approximately 30 minutes. The undiluted (stock), which contains approximately $3.5 x10^5$ copies/mL of the challenge virus, will be diluted further with sterile water for injection, USP to a volume sufficient in order to have the desired challenge dose contained in 1 mL.

One milliliter of the desired challenge strain dose will be added to 80 mL of sterile water for injection, USP in preparation for administration to the study participant. This mixture is termed the final study product use material.

Prior to administration to the participants, an aliquot of the final dilution of the challenge strain will be placed in a freezer tube, labeled according to contents, and kept on wet ice for no longer than 8 hours until stored frozen at ≤600C. This aliquot will be used to confirm the dose of norovirus administered to the participants. Any remaining portion of the thawed aliquot that is not used the day the sample is thawed will be discarded.

The final participant use material (cup) is labeled with the patient's initials and study ID, the time/date of final preparation, an expiration time and date, and the statement "CAUTION- FEDERAL LAW PROHIBITS THE USE OF THIS PRODUCT EXCEPT FOR INVESTIGATIONAL USE". The final patient use material is stored short term at either 2-8°C or held on wet ice for no more than 8 hours.

Once prepared, the challenge dose must be given within 30 minutes. Starting at least 90 minutes prior to administering the challenge virus participants will fast (no solids or liquids by mouth). After fasting, participants will drink 60 mL of a 2% sodium bicarbonate solution. Approximately two minutes later, the CIN-3 norovirus challenge dose will be administered by mouth. Approximately five minutes following administration of the challenge dose, participants will drink 60mL of a 2% sodium bicarbonate solution. After drinking the second 2% sodium bicarbonate solution, participants will fast for 90 minutes.

4.4.6. Blinding

An unblinded study member will review the "secretor" status of participants and prepare a list of participants to be admitted to the inpatient unit for challenge. The participants, the study personnel who perform any study-related assessments, and laboratory personnel performing study assays will be blinded to secretor status.

4.4.7. Prior and Concomitant Therapy

All concomitant medications, taken in the 30 days prior to study enrollment through Day 30 or early termination, whichever occurs first, will be recorded. All prescription and over-the-counter medications as well as vitamins and supplements will be recorded.

Medications which may interfere with the evaluation of the investigational product should not be used unless absolutely necessary. Medications or treatments which are prohibited through study Day 30 include:

- Vaccines (inactivated vaccines, if clinically necessary, should be administered 14 days before or 14 days after challenge)
- Oral, parenteral or high-dose inhaled steroids
- Immunosuppressive or cytotoxic therapy
    - Blood products or immunoglobulins
    - Experimental products (through study Day 180)

Any medications considered for treatment of fever, adverse event, or reactogenicity (solicited adverse events) will be given only at the discretion of the study investigator.

Anti-emetic medication may be administered by PI discretion only. As this would potentially decrease the Vesikari score, anti-emetics only will be used if the participant has reached a high severity of illness and is at risk of requiring intravenous therapy if the emesis is not controlled. Ondansetron - (Orange Book #020781, Zofran® Oral Disintegrating Tablet) or its licensed equivalent may be administered as prescribed by the investigator.

4.4.8. Treatment Compliance

All participants were to receive a single dose of study product administered in the clinic.

4.5. Illness, Infection, Immunogenicity, and Safety Variables

The following sections describe the collection of illness, infection, immunogenicity, and safety variables. See Table 1 for the schedule of study procedures.

4.5.1. Safety Variables

Safety will be assessed by occurrence of AEs through Day 30, SAEs through Day 180, NOCMCs through Day 180, clinical safety lab parameters (WBC, ANC, hemoglobin, platelet count, sodium, potassium, creatinine, ALT, and total bilirubin) through Day 5, and vital sign parameters (blood pressure, oral temperature, and pulse) through Day 6.

Refer to Section 3.3.1 for study definitions of AEs, SAEs, and NOCMCs.

All AEs (laboratory and clinical symptoms) will be assessed by the investigator using a protocol defined grading system. Vital signs will be graded per Table 7 and clinical laboratory measurements will be graded per Table 8. 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 participant'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 relationship of an AE to the administration of study product is made only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator based on all available information at the time of the completion of the eCRF. 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. To help assess, the following guidelines are used.

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

Solicited Adverse Events (Reactogenicity): Solicited Adverse Events are adverse events that are common and known to or expected to occur following the administration of the study product. Participants will be assessed for solicited adverse events following challenge administration and will complete an illness/solicited adverse events memory aid to record symptoms for five days after discharge from the isolation facility. The participant will record the presence and severity, headache, nausea, abdominal cramps/discomfort/pain, abdominal gurgling, abdominal bloating, myalgia, malaise/fatigue, anorexia/loss of appetite, and chills. The participants will be provided with a thermometer. Any symptoms still present after Study Day 10 will continue to be followed until resolution or determined to be stable per investigator discretion. Participants will also be asked to report any medications taken for approximately 30 days following NoV challenge administration and any AEs including any emergency room or other medical visits (other than routine check-ups). The participant illness/solicited adverse events and unsolicited adverse event(s) memory aids will be reviewed with the participant at subsequent visits. Solicited adverse events will be graded per Table 4.

All 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 an Independent Safety Monitor (ISM) (as deemed necessary), the SMC (periodic review unless related), DMID, and the IRB.

All NOCMCs 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 an Independent Safety Monitor (ISM) (as deemed necessary), the SMC (periodic review unless related), DMID, and the IRB.

4.5.2. Illness and Infection Variables

The secretor status of individual participants will be determined based on the detection of histo-blood group antigens (HBGAs) for the secretor antigens (Le b, Le y, H types) versus the non-secretor antigens (Le a and Le x) in their saliva sample collected at the screening visit.

Illness is determined by stool and emesis collection in order to characterize diarrhea and vomiting using the grading scales in Table 5 and the modified Vesikari scale in Table 6. Participants enter the date and time of emesis episodes on an emesis log, and enter the date, time, and consistency of stools on a stool log. Emesis and stool logs are completed through Day 10.

Stool is collected for virus detection during the inpatient period (Day 1 to Day 5) and on follow-up visits (Days 6, 15, 30, 45, and 60 if PCR positive on Day 45). The primary method for norovirus detection in the stool will be qRT-PCR. Genome copies per gram of stool will be determined based on a standard Norovirus GII.4. A sample is considered negative for a detection if the sample produces a Ct value >35 or if no amplification curve was determined. A sample is considered positive if it produces a Ct value <35.

4.5.3. Immunogenicity Variables

Norovirus -specific IgA and IgG results as measured using ELISA will be reported by Dr. Ming Tan's laboratory for serum samples collected pre-challenge and Days 15 and 30 post-challenge. In this assay, the quantity of anti-norovirus IgA or IgG, respectively, is determined by testing a serum specimen in a dilution series. A titer is determined by comparison of the optical density obtained for each dilution of the sample. The titer is equal to the reciprocal of the last dilution of serum that gives a corrected OD value >0.2.

Norovirus GII.4-specific blocking antibodies as measured by receptor blocking assay will be reported by Dr. Ming Tan’s laboratory for serum samples collected pre-challenge and on Days 15 and 30 post-challenge. In this assay, the quantity of anti-norovirus blocking IgG is determined by testing a serum specimen in a dilution series. A blocking titer is determined by comparison of the optical density obtained for each dilution of the sample.

Norovirus specific memory B cell results as measured by ELISpot will be reported for PBMC samples collected pre-challenge and Days 30 and 60 post-challenge. Norovirus antigens are used in this assay to coat 96-well nitrocellulose membrane plates. PBMCs that have been stimulated in-vitro are added to the antigen coated wells and plates are incubated overnight. The number of norovirus antigen specific IgG and IgA secreting memory B cells are detected, along with total IgG and IgA secreting memory B cells. The results are reported as norovirus-specific IgG or IgA secreting memory B cells as a percentage of total IgG or IgA secreting memory B cells.

Norovirus GII.4-specific IgG and IgA ASCs per total IgA and IgG ASCs as enumerated using ELISpot will be reported for PBMC samples collected pre-challenge and Days 6 and 15 post-challenge. Norovirus antigens (expressed capsid proteins referred to as P-particles) are used in this assay to coat 96-well ELISpot plates. PBMCs are added to the coated plates and plates are incubated overnight. The number of IgG and IgA secreting ASCs specific for the P-particles are detected, along with total IgG and IgA ASCs. The results are reported as number of IgG or IgA ASCs per million PBMCs.

5. SAMPLE SIZE CONSIDERATIONS

The anticipated sample size for this study is up to 48 participants, with three cohorts each consisting of 16 challenged participants. The trial is exploratory in nature and thus, is not designed to test a specific hypothesis. The sample size is not based on a power calculation, rather the sample size of approximately 16 per dose group was chosen for feasibility based on the size of the inpatient unit that will be utilized for this study. Table 2 shows the precision of the estimated infection rates for a range of possible infection rates that could be observed in the secretor positive participants in one cohort.

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 participant, and when appropriate by visit number within participant. All summary tables will be structured with a column for each treatment in the order ($3.5x10^3$ copies Secretor Positive, $3.5x10^4$ copies Secretor Positive, $3.5x10^5$ copies Secretor Positive, All Secretor Negative) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

6.2. Timing of Analyses

A CSR will be generated after all primary and secondary endpoint data are available, to include all primary and secondary endpoint data, as well as the data from any available exploratory endpoints. It is anticipated that all exploratory endpoint data will be available at this time.

6.3. Analysis Populations

A tabular listing of all participants, visits, and observations excluded from the efficacy analysis will be provided in the CSR (Listing 5).

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

The mITT population includes all participants who received the challenge study product and contributed both pre- and at least one post-challenge sample during the inpatient period for which a conclusion can be made regarding illness and infectivity.

6.3.2. Per Protocol Population

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

- Data from all available visits for participants found to be ineligible at baseline
- Data from all available visits for participants found to be PCR-positive prior to challenge
- Data from all available visits for participants who do not ingest all of the inoculum
- Data from all visits subsequent to protocol deviations, such as:
  - Receipt of non-study licensed live vaccine through Day 30
  - Long-term use (>2 weeks) of high-dose oral (≥20 mg per day prednisone or equivalent) or parenteral glucocorticoids, or high-dose inhaled steroids for greater than 7 days
  - Receipt of experimental products through Day 180
  - Receipt of parenteral immunoglobulin or blood products within 3 months post challenge
- Data from any visit that occurs substantially out of window
- Data pertaining to norovirus-associated illness after receipt of anti-emetic medication.

Multiple exclusion criteria may apply to a participant or participant-visit, but only one reason will be assigned as the reason for exclusion, prioritized as listed above. The SDCC will prepare a list of population eligibilities from each analysis population. The principal investigator (PI) and scientific lead (SL) will review and confirm all analysis population eligibilities. If no exclusions are made from the PP population, analyses will be presented for the mITT population only.

6.3.3. Safety Population

The Safety Analysis population includes all participants who received at least a partial dose of the challenge study product.

6.4. Covariates and Subgroups

Covariates such as dose, secretor status, and pre-existing antibodies (IgG and IgA) will be used to explore their relationship with illness and infection outcomes.

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

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

As defined in the charter, the SMC will review data at specified times during the course of the study for participant and overall study progress and will conduct ad hoc reviews as appropriate when a halting rule is met or for immediate concerns regarding observations during this study. It is anticipated the SMC will have planned meetings at the following time points:

- Before study initiation
- After each challenge cohort has been completed
- Ad hoc when a halting rule is met or as needed
- At least annually

The SMC will review applicable data to include but not limited to enrollment, demographic, dosing, laboratory and safety data which may include solicited and unsolicited AE/SAEs, concomitant medications,

clinical laboratory values and any physical examinations. As an outcome of each review/meeting, the SMC will make a recommendation as to the advisability to continue, modify or terminate the study. As part of the SMC review between cohorts, the number of participants who achieve illness will be presented by secretor status in the closed session only in order to determine which dose to administer in the following cohort.

An interim immunogenicity review will be performed after the second cohort to determine if there is a correlation between anti-norovirus GII.4 serum IgG by ELISA and/or blocking assay (protective antibody titers) and illness rate. If anti-norovirus GII.4 serum IgG by ELISA and/or blocking assay correlates to incidence of illness, then the eligibility criteria will be revised for the final cohort to exclude people at low risk for norovirus infection.

If an ad hoc meeting is convened, the SMC may be asked to review solicited and unsolicited AE/SAEs, concomitant medications, clinical laboratory values and any physical examinations.

The medical monitor is empowered to stop study enrollment and/or study procedures if adverse events that meet the halting criteria are reported. The medical monitor and the ISM will be responsible for reviewing SAEs in real time. The SMC will review SAEs on a regular basis and ad hoc during the study.

Final review meeting: 6 to 8 months after clinical database lock to review the cumulative unblinded safety data for the study. The data will be provided in a standard summary format. The SMC may be asked to provide recommendations in response to questions posed by the IND sponsor.

No formal interim analyses are planned, and as such, no adjustments for multiple testing will be conducted.

6.7. Multicenter Studies

Not applicable. This study is conducted at a single site.

6.8. Multiple Comparisons/Multiplicity

This study was designed to determine the optimal dose of an experimental human norovirus GII.4 challenge strain to be used in future trials. The study was not designed to test any specific null hypothesis, and as such no adjustment for multiple comparisons will be performed.

7. STUDY PARTICIPANTS

7.1. Disposition of Participants

Table 12 will present a summary of the reasons that participants were screened but not enrolled.

The composition of analysis populations, including reasons for participant exclusion, by treatment group, is presented in Table 10. A listing of participants excluded from analysis populations will be provided in Listing 5.

The disposition of participants in the study will be tabulated by treatment group (Table 9). The table shows the total number of participants screened, enrolled, receiving challenge, completing the inpatient period, completing all blood draws, completing all stool collections, and the number completing the study.

A flowchart showing the disposition of study participants, adapted from the Consort Statement [13] will be included (Figure 2). This figure will present the number of participants screened, enrolled, lost to follow-up, and analyzed, by treatment arm.

The dates of challenge administration by treatment group are provided in Table 11. A listing of participants who terminated from study follow-up and the reason will be included in Listing 2.

A listing of the actual dosages administered for each cohort as determined through dose verification is provided in Listing 8.

7.2. Protocol Deviations

A summary of participant-specific protocol deviations will be presented by the deviation category, deviation type, and treatment group for all participants (Table 3). Deviations that are considered major deviations that will be reviewed for possible participant exclusion from the per protocol population include, but are not limited to: eligibility/enrollment, product administration deviations, out of window visits. All participant-specific protocol deviations and non-participant specific protocol deviations will be included in Appendix 3 as data listings (Listing 3 and Listing 4, respectively).

8. ILLNESS AND INFECTION EVALUATION

This trial is exploratory in nature and thus, is not designed to test a specific hypothesis. Rather, it is intended to estimate illness (and therefore, infection) rates for up to three different challenge doses to determine the optimal dose of an experimental human norovirus GII.4 challenge strain to be used in future trials testing candidate vaccines and/or therapeutics.

Illness and infection data summaries will be presented for the mITT and PP populations. Analyses will be presented by cohort dose group for secretor positive participants, with the secretor negative participants from all cohorts pooled into one group.

8.1. Primary Illness and Infection Analysis

8.1.1. Primary Analysis

The primary endpoint to assess the primary objective is the occurrence of norovirus-associated illness (vomiting, diarrhea, and positive PCR) in secretor positive participants through Day 4 after challenge. It is anticipated that participants will meet the criteria to be discharged on Day 5; nevertheless, all data available through discharge will be included for this endpoint. The number and percentage of participants with norovirus-associated illness will be summarized by dose group along with corresponding two-sided exact (Wilson-Score) 95% confidence intervals in Table 16.

8.1.2. Supplementary Analysis

A logistic regression model of norovirus-associated illness, as a function of log-dose, will be constructed to select a recommended dose for future studies:

$$\ln(p/(1-p)) = \beta_1 x + \beta_0,$$

where p is the proportion of secretor positive participants with norovirus-associated illness and x is the $\log_{10}$ of the challenge dose. The dose at which 50% of participants achieve illness will be calculated by setting p=0.5 and solving for x using the estimates for β_0 and β_1. Coefficient estimates along with the estimate dose for the mITT and PP populations will be displayed in Table 17.

Example SAS code:

```
proc logistic data=ds

      model aval(event='1') = trtlog;

      ods output parameterestimates=estout;

run;
```

8.2. Secondary Illness and Infection Analyses

8.2.1. Infection through Day 30

For the secondary endpoint of the number of participants with infection through Day 30, infection will be defined by:

- Detection of norovirus GII.4 in stool by qRT-PCR at Days 2, 3, 4, 5, 6, 15, or 30; or
- ≥4-fold rise from baseline in GII.4-specific antibody titers in serum IgG by ELISA through Day 30

The number, percentage, and corresponding two-sided exact (Wilson-Score) 95% confidence intervals will be presented by treatment group in Table 18 for the mITT population and in Table 19 for the PP population. A listing of individual qRT-PCR data by participant and time point will be provided in Listing 9.

8.2.2. Peak Genome Equivalent Copies/g of Virus in Stool through Day 60

The peak GEC/g as defined in Section 3.3.2 will be summarized by tabulating the number of observations, mean, standard deviation, and 95% CI of the geometric mean, minimum, and maximum in Table 20 and Table 21.

8.2.3. Duration (days) of Viral Secretion through Day 60

Summary statistics will include the number of participants shedding for at least one day, the mean and standard deviation of the duration, as well as the median and range of duration as shown in Table 20 and Table 21. The interquartile range (IQR), or the difference between the 75^{th} and 25^{th} percentiles, will be presented as a measure of variability due to the skewed distribution and small sample size expected for the duration.

8.2.4. Modified Vesikari Score through Day 4

The distribution of points for each component will be presented in Table 22 and Table 23 for the mITT and PP population, respectively. Summary statistics for the total score by treatment group will be presented in Table 24. The protocol states that scores will be tested to examine if there is a relationship between Vesikari scores and challenge dose; however, as the study is not powered for formal hypothesis testing between dose groups, this relationship will be examined descriptively through box plots. These will be presented in Figure 3 and Figure 4.

8.2.5. Duration (hours) of Vomiting and/or Diarrhea through Day 5

Summary statistics will be presented by treatment group including the number of participants for whom the duration in hours could be calculated; as well as the mean, standard deviation, median, and range of duration. These will be presented in the mITT and PP population in Table 25 and Table 26.

8.3. Exploratory Illness and Infection Analyses

8.3.1. Quantity and Duration of Virus Shedding in Stool by qRT-PCR

An exploratory analysis of interest is to use longitudinal methods to explore the possibility of determining not just the presence of virus, but to estimate trends in the magnitude of virus shed over time. A population-averaged model for nonnormal repeated measurements will be employed. Due to the nature of quantitative PCR data that is often skewed and strictly positive, a gamma distribution will be assumed for the $\log_{10}$-transformed response variable. The model will include dose group and time (scheduled post-baseline visit) as fixed-effect categorical factors and a dose group*time interaction term. The dose group*time interaction allows the difference between dose groups to change over time but may be removed from the final model if found to be non-significant ($p<0.05$). The fixed-effect of time will be modeled as a categorical (class) variable to allow for an unstructured relationship between time and response, as opposed to a linear one. A compound symmetric working correlation matrix will be assumed. The purpose of the model is to visually examine the magnitude of virus shed over time rather than to test for differences in dose groups, as such, no hypothesis tests with respect to dose group will be conducted. The model will be restricted to secretor positive

participants. A plot of the estimated population regression model for the final reduced model will be presented in Figure 5 and Figure 6.

Example SAS code:

```
proc genmod data=ds;
      class trtpn visit usubjid;
      model lresult = trtpn visit trtpn*visit / dist=gamma link=log obstats pscale;
      repeated subject=usubjid / type=cs corrw covb modelse;
      ods output obstats=outlog;
run;
```

9. SAFETY EVALUATION

All summaries and analysis of safety data will be presented for the Safety Analysis Population. Safety summaries will be presented overall and by treatment group.

Listings will be sorted by treatment group, participant ID, parameter (if applicable), and visit.

Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. All categorical measures will be summarized by the frequency and percentages (based on the non-missing sample size) of observed levels.

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, ethnicity, and race will be presented by treatment group and overall (Table 13 and Table 14) for all enrolled participants. Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, participants may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual participant listings (Appendix 3) will be presented for all demographics (Listing 6).

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 25.0 or higher.

Summaries of participants' pre-existing medical conditions will be presented by treatment group (Table 15).

Individual participant listings will be presented for all medical conditions (Listing 7).

9.1.2. Prior and Concomitant Medications

Prior and concomitant medications will be coded to the Anatomical Therapeutic Classification (ATC) using the WHO Drug Dictionary. A summary of all prior and concomitant medications will be presented by ATC1 and ATC2 code and treatment group for the safety population (Table 100).

Individual participant listings will be presented for all concomitant medications (Listing 22).

9.2. Measurements of Treatment Compliance

All participants were to receive a single dose of study product administered in the clinic. Any participants who were enrolled but not challenged will be presented by treatment group as part of the participant disposition table (Table 9).

9.3. Adverse Events

When calculating the incidence of adverse events (i.e., on a per participant basis), each participant will only be counted once and any repetitions of adverse events within a participant will be ignored; the denominator will be the total number of participants in the safety population. All adverse events reported will be included in the summaries and analyses.

An overall summary of adverse events is presented in Table 47. A summary of adverse events occurring in at least 5% of participants is presented in Table 48.

9.3.1. Solicited Events and Symptoms

Systemic solicited adverse events were collected pre-challenge, post-challenge, and via memory aid through 5 days after discharge from the isolation facility and graded on a scale of 0 (absent), 1 (mild), 2 (moderate) and 3 (severe). Systemic events include headache, nausea, abdominal cramps/discomfort/pain, abdominal gurgling, abdominal bloating, myalgia, malaise/fatigue, anorexia/loss of appetite, and chills. Grading scales for all solicited events and symptoms, subjective and objective, are included in Table 4.

The proportion of participants reporting at least one solicited adverse event will be summarized for each solicited adverse event and any systemic symptom. Exact (Clopper-Pearson) two-sided 95% CIs will be presented by treatment group (Table 49).

For each systemic event and any systemic event, the maximum severity per participant over 10 days after challenge will be summarized for the safety population. The number and percentage of participants reporting each event will be summarized by severity grading (none, mild, moderate, severe, not reported) and treatment group. For each event the denominator is the number of participants with non-missing data for the specific event (Table 50).

Additionally, solicited AEs will be analyzed by taking the most severe response over the 10-day follow-up period, dichotomizing into a binary variable (none versus mild, moderate, or severe) and summarized by treatment group (Table 51). A logistic regression model will be fit to estimate the effect of treatment group on the probability of reporting any mild, moderate, or severe systemic event (Table 52).

The number of participants reporting a solicited adverse event in each cohort will be summarized for each day post-challenge by severity grading both in a summary table (Table 53, Table 54, Table 55, and Table 56) and graphically in a bar chart (Figure 15, Figure 16, Figure 17, and Figure 18).

Solicited adverse events by participant will be presented in Listing 13, Listing 14, and Listing 15.

9.3.2. Unsolicited Adverse Events

The proportion of participants reporting at least one unsolicited adverse event will be summarized by MedDRA system organ class and preferred term. Denominators for percentages are the number of participants in the safety population.

Adverse events by participant will be presented in Listing 16.

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

- Participant incidence and total frequency of adverse events over time with exact (Clopper-Pearson) two-sided 95% CIs (Days 1-10, Days 11-30, Days 31-180, and anytime post-challenge (Table 57, Table 58, Table 59, and Table 60);
- Summary of severity and relationship to study product (Table 61, Table 62, Table 63, Table 64, Table 65);
- Participant incidence and total frequency of related adverse events within 10 days post-challenge (Table 66);
- Participant incidence and exact (Clopper-Pearson) two-sided 95% CIs of Grade 3 (severe) unsolicited AEs through Day 30 (Table 67);
- Participant listing of serious adverse events (Table 68);

- Participant listing of non-serious adverse events of moderate or greater severity (Table 69);
- Participant listing of new onset chronic medical conditions (Table 70);
- Bar chart of related adverse events by MedDRA SOC and severity (Figure 19, Figure 20, Figure 21, and Figure 22);
- Bar chart of the incidence of related adverse events by MedDRA SOC and maximum severity (Figure 23, Figure 24, Figure 25, and Figure 26).

For the secondary endpoint of the number of SAEs through Day 180, the number and percentage of participants in each group along with exact Clopper-Pearson 95% CIs will be presented within the text of the results section of the CSR.

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

The following listings will be presented including Participant ID, Adverse Event Description, Days Post-Challenge and Duration, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, and Outcome:

- Deaths and Serious Adverse Events (Table 68);
- New Onset Chronic Medical Conditions. (Table 70)

9.5. Pregnancies

For any participants in the safety population who became pregnant during the study, every attempt was made to follow these participants to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A listing of pregnancies and outcomes will be presented (Listing 23, Listing 24, Listing 25, Listing 26 and Listing 27).

9.6. Clinical Laboratory Evaluations

Clinical laboratory evaluations are conducted at screening and during the inpatient period if indicated per investigator discretion. Hematology parameters include white blood cells (WBC) with neutrophils (ANC), hemoglobin, and platelet count. Serum chemistry parameters include alanine transaminase (ALT), total bilirubin, creatinine, potassium, and sodium. Urinalysis parameters include urine protein.

If at least one participant has safety chemistry labs drawn post-challenge administration, then the distribution of chemistry results by severity, time point, and treatment group will be presented in Table 74, Table 75, Table 76, Table 77, Table 78, and Table 79. If at least one participant has safety hematology labs drawn post-challenge administration, then the distribution of hematology results by severity, time point, and treatment group will be presented in Table 85, Table 86, Table 87, Table 88, and Table 89. If at least one participant has safety urinalysis done post-challenge administration, then the distribution of urinalysis results by severity, time point, and treatment group will be presented in Table 94. The baseline time point will be defined as the last measurement prior to challenge.

Descriptive statistics including mean, standard deviation, median, minimum and maximum values by time point, for each laboratory parameter, will be summarized in Table 80, Table 81, Table 82, Table 83, and Table 84 for chemistry parameters; and in Table 90, Table 91, Table 92, and Table 93 for hematology parameters.

Participant visits with abnormal laboratory results, Grade 1 severity or higher, will be presented in Table 71, Table 72, and Table 73.

Listing 17, Listing 18, and Listing 19 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 systolic blood pressure, diastolic blood pressure, pulse, and oral temperature. Vital signs were assessed at screening, daily during the inpatient period (Day 1- Day 5), Day 6, and if clinically indicated, at Days 15, 30, 45, and 60. Vital signs will be tabulated by time point and treatment group (Table 91, Table 92, Table 93, Table 94, and Table 95; Listing 20). The baseline time point will be defined as the last measurement prior to challenge. For post-baseline time points, if multiple assessments are taken at a visit, the last assessment will be used in summary tables of maximum severity, however all assessments will be presented in the listing.

An abbreviated physical examination is performed at screening and a symptom directed physical examination may be performed at all other study visits if clinically indicated. The following body systems will be assessed: Abdomen, Cardiovascular/heart, Extremities, General Appearance, HEENT, Lymph nodes, Musculoskeletal, Neck, Neurological, Pulmonary/Chest, and Skin (Listing 21).

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification (ATC) using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-participant listing of all prior and concomitant medication use will be presented (Listing 22). A summary of prior and concurrent medications will be presented by ATC1, ATC2 code, and treatment group for the safety population (Table 100). Any medications reported that were stopped more than 30 days prior to enrollment or started after Day 30 will be excluded from the summary but displayed in the listing.

9.9. Other Safety Measures

Not applicable.

10. PHARMACOKINETICS

Not applicable.

11. IMMUNOGENICITY

Immunogenicity data summaries and analysis for exploratory objectives and endpoints will be presented for the mITT and PP populations. In general, for assays in which the data are assumed to be log-normally distributed, the geometric mean and 95% confidence interval, along with the minimum and maximum values will be presented. For assays with a pre-specified definition for responders (e.g., ≥4-fold rise), the percentage of participants defined as responders and 95% CIs, as well as geometric mean fold rise (GMFRs) and 95% CIs will be presented. Exact (Clopper-Pearson) CIs will be used for proportional endpoints.

Data listings of immunogenicity results as reported by the laboratory will be provided in Listing 10, Listing 11 and Listing 12. Listings will be sorted by treatment group, participant identifier, and visit.

11.1. Primary Immunogenicity Analysis

There are no primary immunogenicity endpoints listed for this study.

11.2. Secondary Immunogenicity Analysis

There are no secondary immunogenicity endpoints listed for this study.

11.3. Exploratory Immunogenicity Analysis

11.3.1. GII.4-specific Antibody Titers in Serum by ELISA

Summaries will be presented in Table 27 and Table 28 for IgA, in Table 29 and Table 30 for IgG, and in Table 31 and Table 32 for blocking antibody.

The number of participants with ≥4-fold rise from baseline in GII.4-specific antibody titers in serum at Days 15 and 30 will be presented in Table 33 and Table 34 for IgA, in Table 35 and Table 36 for IgG, and in Table 37 and Table 38 for blocking antibody.

Reverse cumulative distribution (RCD) curves will be presented for GII.4-specific serum IgA, IgG, and blockade antibody titers. Plots for each assay will be generated with a separate panel for each time point, and separate curves within each panel for each treatment group, as shown in Figure 7 through Figure 12.

11.3.2. Baseline NoV GII.4 Serum IgG, IgA, and Blocking Antibody Titers in Participants with and without Infection

The association between baseline norovirus GII.4 serum antibody titers and infection status will be presented in Table 39 and Table 40. The pre-challenge GMT and 95% CI will be presented for each assay and treatment group stratified by infection status. These results will be examined graphically by looking at the distribution of pre-existing antibodies by infection status in Figure 13 and Figure 14. If there is any suggestion of a relationship between pre-existing antibodies and response, this will be modeled using logistic regression to estimate the relationship between infection and illness rates and pre-existing antibody level.

11.3.3. Norovirus GII.4-specific Memory B Cells by ELISpot

The percentage of Norovirus-specific IgG or IgA secreting memory B cells out of total IgG or IgA secreting memory B cells at baseline and Days 30 and 60 will be summarized by time point and treatment group using descriptive statistics in Table 41 and Table 42.

11.3.4. Norovirus GII.4-specific IgA and IgG ASCs per Total IgA- or IgG-Secreting ASCs

Summary statistics including the number of participants with a valid result, mean and standard deviation, median, and range will be provided for the number of GII.4-specific IgA and IgG ASCs, total IgA and IgG ASCs, and the ratio of GII.4-specific IgA/IgG ASCs over total IgA/IgG ASCs by time point and treatment group in Table 43, Table 44, Table 45, and Table 46. As an additional exploratory analysis, the percentage of participants with >0 GII.4-specific ASCs will be presented for IgA and IgG separately.

11.3.5. Norovirus GII.4-specific IgA and IgG ALS by ELISA

This endpoint will not be included in the CSR as this assay was not performed for this study. Please see Section 15 for additional details.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. If the original data are not reported to a consistent number of decimal places, the statistics will be reported to 1 decimal place greater than the minimum number of decimal places in 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%. For immunogenicity results presented as percentages, e.g. percentage of cells, decimal places used for reporting may vary depending on the precision of the particular assay. 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

The exploratory outcome measure, "Norovirus GII.4-specific IgA and IgG ALS by ELISA baseline and at Days 6 and 15," for the exploratory objective of "Determine total and norovirus GII.4 -specific IgA- and IgG-Antibody Secreting Cells (ASCs) by ELISpot assay and Antibody Lymphocyte Supernatant (ALS) by ELISA" will not be presented in the CSR as the ALS assay is no longer planned to be performed. Since ASC and ALS assays provide similar results, it was elected to only do ASC testing due to budget constraints.

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 Illness, Infection, Immunogenicity, and Safety Measurements Assessed and Flow Chart

Table 1: Schedule of Study Procedures

	Outpatient Screening		Inpatient Challenge Admission					Outpatient Follow-Up					Final Study Contact
Study Day	Day -60 to Day -2 Visit 00A [$]	Day -1 Visit 00B[$]	Day 1 Visit 01	Day 2 Visit 02	Day 3 Visit 03	Day 4 Visit 04	Day 5* Visit 05	Day 6+2 clinic visit Visit06	Day 15+/-1 clinic visit Visit 07	Day 30 -2/+5 clinic visit Visit 08	Day 45+/-5 clinic visit Visit 09	Day 60+/-5 clinic visit Visit 10	Day 180+/-14 study contact visit Visit 11
Informed Consent	X	(X)	(X)										
Test Of Understanding[!]	X	(X)	(X)										
Medical History/ (Demographics at screening)	X	X	(X)					X	X	X	X	X	X
Concomitant Medication History[1] or Review	X	X	(X)	X	X	X	X	X	X	X			
I/E Criteria Review	X	X	X										
Physical Examination (Abbreviated) [#]	X												
Clinical Assessment/Symptom Directed PE[2]		X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	
Monitor/Record Fluid Input/Output (I/Os) [=]				X	X	X	X						
Vital Signs[3,4]	X	X	X[4]	X	X	X	X	X	(X)	(X)	(X)	(X)	
Body Weight[5]	X	X	(X)	(X)	(X)	(X)	(X)						
Chemistry[6, 8]	X		(X)	(X)	(X)	(X)	(X)						
Hematology[7, 8]	X		(X)	(X)	(X)	(X)	(X)						
Urinalysis[9]	X		(X)	(X)	(X)	(X)	(X)						
Urine opiate screen	X												
Urine or serum Pregnancy Test (females of childbearing potential)	X	X	(X)										
HIV, HepB surface Ag, Hep C Ab	X												
COVID-19 antigen test		X											
Serum norovirus antibody (IgG, and IgA ELISA and blocking antibody)		X	(X)						X	X			
RNAseq assay (PAXgene) Future Use		X	(X)	X		X		X	X	X			

	Outpatient Screening		Inpatient Challenge Admission					Outpatient Follow-Up					Final Study Contact
Study Day	Day -60 to Day -2 Visit 00A [$]	Day -1 Visit 00B[$]	Day 1 Visit 01	Day 2 Visit 02	Day 3 Visit 03	Day 4 Visit 04	Day 5* Visit 05	Day 6+2 clinic visit Visit06	Day 15+/-1 clinic visit Visit 07	Day 30 -2/+5 clinic visit Visit 08	Day 45+/-5 clinic visit Visit 09	Day 60+/-5 clinic visit Visit 10	Day 180+/-14 study contact visit Visit 11
Blood for cytokine by Luminex assays (plasma) Future Use		X	(X)	X		X		X	X				
Blood for DC/NK (PBMC) Future Use		X	(X)	X		X		X	X				
Norovirus GII.4 -specific Memory B cells/ELISpot assay (PBMC)		X	(X)							X		X	
Norovirus GII.4 -specific T cell/intracellular cytokine assay (PBMC) Future Use		X	(X)					X	X	X			
Norovirus GII.4 -specific ASC ELISpot and ALS ELISA		X	(X)					X	X				
Saliva for secretor status [10] (phenotype)	X												
Stool collection system ("stool kit") and instructions provided		X	X	X	X	X	X	X	X	X	X		
Fecal IgA (Future Use) *** ****		X	(X)	X		X		X	X	X			
Stool Collection for shedding of norovirus PCR[11, 12 □]		X	X	X	X	X	X	X	X	X	X	X□	
Stool Collection for microbiomes (Future Use)[12****]		X	(X)	X		X		X	X	X			
Stool Collection for cytokines (Future Use)[12]		X	(X)	X		X		X	X	X			
Challenge Administration[13]			X										
Solicited Adverse Events Assessments			X	X	X	X	X						
Illness/Solicited Adverse Events Memory Aids[14^]							X^	X^	X^	X^			
Adverse Event Monitoring[15]			X	X	X	X	X	X	X	X	X	X	X
Discharge from Inpatient Facility (if discharge criteria met)							X+						

1. On Day 1, confirm that the participant has not taken any prohibited medications prior to challenge. All concomitant medications taken in the 30 days prior to study enrollment through Day 30 or early termination will be recorded.

	Outpatient Screening		Inpatient Challenge Admission					Outpatient Follow-Up					Final Study Contact
Study Day	Day -60 to Day -2 Visit 00A [$]	Day -1 Visit 00B[$]	Day 1 Visit 01	Day 2 Visit 02	Day 3 Visit 03	Day 4 Visit 04	Day 5* Visit 05	Day 6+2 clinic visit Visit06	Day 15+/-1 clinic visit Visit 07	Day 30 -2/+5 clinic visit Visit 08	Day 45+/-5 clinic visit Visit 09	Day 60+/-5 clinic visit Visit 10	Day 180+/-14 study contact visit Visit 11

2. Symptom directed physical examination.
3. Vital Signs include blood pressure, pulse, and oral temperature. They will be taken daily during the inpatient challenge unless otherwise specified in the protocol or if medically indicated.
4. Vital signs will be obtained prior to challenge administration on Day 1 and approximately 30 and 60 minutes after receipt of the challenge virus, and more frequently if medically indicated.
5. Weight will be checked at screen and baseline, prior to challenge. Weight will be obtained at other times as clinically indicated.
6. Serum chemistry parameters include alanine transaminase (ALT), total bilirubin, creatinine, potassium, sodium.
7. Hematology parameters include white blood cells (WBC) with neutrophils (ANC), hemoglobin, and platelet count.
8. Screening labs (chemistry and hematology) will be repeated if original labs obtained more than 60 days before challenge. Participants who receive IV hydration during the inpatient admission will have safety labs collected, if indicated per investigator discretion and will be required to have clinically acceptable electrolyte values for sodium and potassium prior to discharge.
9. Urinalysis parameters include urine protein. At the discretion of the investigator or delegate participants may have a urine specific gravity performed to capture urine results in real time.
10. Saliva for secretor status at screening. If available, results from previous testing for secretor status may be used for screen and need not be repeated.
11. A rectal swab may be used for detection of Norovirus shedding, if a bulk stool cannot be provided.
12. One stool sample will be collected on Day -1 or Day 1 baseline, prior to challenge. If additional stool is produced by a participant after the initial sample but prior to challenge, the sample will not be collected nor entered to Global Trace. After challenge, stools will be collected as described in the MOP. At least 2 aliquots from each stool collected while inpatient will be processed for norovirus shedding. Samples also will be collected and stored for microbiome testing. Stool samples for microbiome testing, cytokine detection, and fecal IgA must be bulk samples.
13. Participants may have clear liquids within 4 hours of challenge but will be NPO (nothing by mouth) for 90 minutes before and for 90 minutes after challenge administration.
14. Participants will complete a daily memory aid of illness/solicited events symptoms, changes in medical status, and concomitant medications. Participant's memory aids will be reviewed at the Day 6 visit. Study staff will attempt to collect and retain the illness/solicited events memory aid at the Day 15 visit.
15. Adverse events will be collected to Day 30. Adverse events limited to new-onset chronic medical conditions and Serious Adverse Events will be collected up to Day 180.

(X) Represents study related procedures that are not required but *may* be done on this day, if indicated. (i.e. Participants may be admitted the day before challenge or on the day of challenge. Some study related procedures may occur within 24 hours of challenge.).

* Participants needing to remain past Day 5 will have study evaluations repeated daily until discharge.

*** Efforts will be made to collect 2 baseline bulk samples prior to challenge, including morning of challenge.

**** Since fecal IgA stools will be sent to the Fisher Repository, and then microbiome samples can be sent to the repository as well. Samples may be collected together (with appropriate vials) as microbiome and fecal IgA samples for future use with appropriate collection days.

▫ Participants who continue to shed Norovirus at the Day 60 visit will be followed for clearance.

!! Participants will be provided with educational materials at screening and given complete education about study participation. A sample test may be given during the education process. If a participant does not score a 70% on the exam, he/she may re-take the test.

\# An abbreviated physical examination is distinguished from a complete physical exam in that all assessments are not required (e.g. genito-urinary and rectal exams).

= All emesis will be measured. All stools will be graded for consistency, and all loose or watery stools (i.e., those that conform to the shape of the container) also will be weighed. Participants who develop diarrhea will be asked to drink 1.5 mL of ORS for each gram of diarrheal stool that they produce. Participants developing vomiting will be asked to drink a volume of ORS equivalent to the amount of the emesis.

$ Screening evaluations may occur over 1 or more visits.

\+ Participants will be provided instructions and "stool kit" to collect sample.

@ Provide participant with digital thermometer and instructions in its use and asked to take and record their oral temperature once daily at the same time each day for 5 days after discharge.

^ Remind/review with participants to contact the site if a household contact or anyone they have daily contact with develops symptoms of Norovirus infection within a week after being discharged from the inpatient unit.

9.7.1 Sample Size

Table 2: Sample Size/Probability Estimates

Number with illness	Observed Illness Rate	95% Exact CI
0	0	(0.00, 0.21)
2	0.125	(0.02, 0.38)
4	0.25	(0.07, 0.52)
6	0.375	(0.15, 0.65)
8	0.5	(0.25, 0.75)
10	0.625	(0.35, 0.85)
12	0.75	(0.48, 0.93)
14	0.875	(0.62, 0.98)
16	1	(0.79,1.00)

10.2 Protocol Deviations

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

[Implementation Note: Only display the Deviation Types that were reported in the study.]

Category	Deviation Type	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)		Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)		Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)		All Cohorts Secretor Negative (N=X)		All Participants (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	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	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										

Category	Deviation Type	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)		Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)		Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)		All Cohorts Secretor Negative (N=X)		All Participants (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
	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										

N = Number of participants in the Safety Population

12.2.2 Displays of Adverse Events

Table 4: Solicited Adverse Event Grading Scale

Clinical Feature	Grade 0	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Fever (oral temperature)	none	100.4 – 101.1˚F (38.0 – 38.4°C)	101.2 – 102.0˚F (38.5 – 38.9°C)	>102^0F (>38.9°C) or ER visit or hospitalization
Headache	none	no pain medications taken	use of pain medication required	narcotic pain med required and/or prevents daily activity
Nausea	none	mild*	moderate**	severe***
Abdominal Cramps/discomfort/pain	none	mild*	moderate**	severe***
Abdominal gurgling	none	mild*	moderate**	severe***
Abdominal bloating	none	mild*	moderate**	severe***
Myalgia	none	mild*	moderate**	severe***
Malaise, fatigue	none	mild*	moderate**	severe***
Anorexia, loss of appetite	none	mild*	moderate**	severe***
Chills	none	mild*	moderate**	severe***

Notes:
*Mild = No interference with activity
**Moderate = Some interference with activity
***Severe = Significant interference, prevents daily activity

Table 5: Diarrhea/Vomiting Grading Scale

Clinical Feature	Grade 0	Grade 1	Grade 2	Grade 3
Diarrhea	None	In a 24/h period: 3 loose stools or liquid stools **or** 300-599 gm of loose or liquid stool	In a 24/h period: 4-5 loose stools or liquid stools **or** 600-800 gm of loose or liquid stool	In a 24/h period: ≥6 liquid stools **or** >800 gm of loose or liquid stool
Vomiting	None	1-2 episodes in 24 hours	3-5 episodes in 24 hours	>5 episodes in 24 hours

Notes: Stool consistency is determined according to the following guide: Normal= Firm, tootsie roll consistency, soft pudding consistency; Loose = Runny, takes the shape of the container, gravy consistency, brown liquid, opaque liquid, chocolate milk consistency; Liquid/Watery = Clear liquid, rice water, soapy water consistency.
≤2 loose or liquid stools or <300 gm stool in a 24h period are not diarrhea.

Table 6: Modified Vesikari Score (17 Point Scale)

Duration of Diarrhea (days)	**Points**
1	1
2-3	2
≥4	3
Maximum Number of Diarrheal Stools/ 24 hours	
3	1
4-5	2
≥6	3
Duration of Vomiting (days)	
1	1
2	2
≥3	3
Maximum Number of Vomiting Episodes/ 24 hours	
0	0
1	1
2-4	2
≥5	3
Fever (°C)	
≤37	0
37.1-38.4	1
38.5-38.9	2
≥ 39	3
Dehydration	
None	0
IV Treatment	2

Table 7: Vital Signs Adverse Event Grading Scale

Adverse Event	Severity	Parameter
Fever	1	38.0 – 38.4°C 100.4 – 101.1°F
	2	38.5 – 38.9°C 101.2 – 102.0°F
	3	>38.9°C >102°F or ER visit or hospitalization
Hypertension (systolic)}	1	151-155 mm Hg
	2	156-160 mm Hg
	3	>160mm Hg or ER visit or hospitalization
Hypertension (diastolic)	1	91 – 95 mm Hg
	2	96-100 mm Hg
	3	>100 mm Hg or ER visit or hospitalization
Hypotension (systolic)	1	85-89 mm Hg
	2	80-84 mm Hg
	3	<80 mm Hg or ER visit or hospitalization
Bradycardia*	1	45-50bpm *
	2	40-44 bpm
	3	<40 bpm or ER visit or hospitalization
Tachycardia	1	101-115 bpm
	2	116-130 bpm
	3	>130 bpm or ER visit or hospitalization

* If participant baseline heart rate is <45 beats per minute and the investigator determines that this is not clinically significant (e.g., athletes) and heart rate increases >45 beats per minute on moderate exercise (two flights of stairs), this will not be considered a grade 1 adverse event. If a participant has significant abnormalities in their heart rate, they will be informed of the values and advised to seek care from their physician.

} If a participant has significant abnormalities in their blood pressure, they will be informed of the values and advised to seek care from their physician.

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 8: Laboratory Adverse Event Grading Scale

Laboratory	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Sodium, low, mEq/L	132 – 135	130 – 131	125 – 129
Sodium, high, mEq/L	146 – 147	148 – 149	150 or greater
Potassium, high, mEq/L	5.2 – 5.3	5.4 – 5.5	5.6 – 5.7
Potassium, low, mEq/L	3.3 – 3.4	3.1 – 3.2	2.9 – 3.0
Creatinine, high mg/dL (female)	1.0 - 1.1	1.2 - 2.0	2.1 – 2.5
Creatinine, high mg/dL (male)	1.2 – 1.3	1.4 – 2.0	2.1 – 2.5
Liver Function Tests (ALT) increase by factor	>1.1-2.5 x ULN	>2.5-5.0 x ULN	>5.0x ULN
Total bilirubin	>1.0-1.5 x ULN	>1.5-2.0 x ULN	>2.0 x ULN
Hgb (female), low g/dL	10.9-11.6	9.4 – 10.8	≤9.3
Hgb (male), low g/dL	13.1-13.2	12.5-13.0	≤12.4
WBC, increase, cells, x 10^3u/L	>11.1 –≤15.0	>15 - ≤ 20	>20.0
WBC, decrease, cells, x 10^3u/L	2.5-<4.4	1.5-<2.5	<1.5
Absolute Neutrophil Count (ANC), x 10^3u/L	1.2-<1.7	0.9-<1.2	<0.9
Platelets, decrease, cells/mm^3	124,000-<134,000	100,000<124,000	<100,000
Urine protein	Trace	1+	2+

14.1 Description of Study Participants

14.1.1 Disposition of Participants

Table 9: Participant Disposition by Treatment Group

Participant Disposition	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)		Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)		Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)		All Cohorts Secretor Negative (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%
Screened	--	--	--	--	--	--	--	--	x	--
Enrolled	x	100	x	100	x	100	x	100	x	100
Received Challenge	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Inpatient Period	x	xx	x	xx	x	xx	x	xx	x	xx
Completed All Blood Draws[a]										
Completed All Stool Collections[b]										
Completed Follow-up (Study Day 180)[c]										
Completed Per Protocol[d]										

Notes: N = Number of participants enrolled
[a] Includes blood draws for serum norovirus antibody through Day 30.
[b] Includes stool collection for shedding of norovirus through Day 60.
[c] Refer to Listing 16.2.1 for reasons participants terminated early.
[d] Refer to Listing 16.2.3 for reasons participants are excluded from analysis populations.

Table 10: Analysis Population Eligibilities by Treatment Group

Analysis Population	Eligibility Category	Reason Participants Excluded	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)		Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)		Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)		All Cohorts Secretor Negative (N=X)		All Participants (N=X)	
			n	%	n	%	n	%	n	%	%	n
Safety Population	Eligible		x	xx	x	xx	x	xx	x	xx	x	xx
	Excluded	Any Reason										
		Did not receive any challenge product										
Modified Intention-to-Treat Population	Eligible											
	Excluded	Any Reason										
		Did not receive any challenge product										
		Did not contribute a pre-challenge sample										
		Did not contribute a post-challenge sample										
Per Protocol Population	Eligible											
	Excluded	Any Reason										
		Found to be ineligible at baseline										
		Did not receive any challenge product										
		Did not ingest all of the inoculum										
		Did not contribute a pre-challenge sample										
		Did not contribute a post-challenge sample										

N = Number of participants enrolled.

Table 11: Dates of Challenge Administration by Treatment Group

Date of Challenge	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)	All Participants (N=X)
Total (Entire period of enrollment)	x	x	x	x	x
DDMMMYYYY	x	x	x	x	x
DDMMMYYYY					
DDMMMYYYY					
DDMMMYYYY					
N = Number of participants enrolled.					

Table 12: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of participants 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 participant.
[b] Denominator for percentages is the total number of participants who were screened but not enrolled.

14.1.2 Demographic Data by Study Group

Table 13: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group, All Enrolled Participants

Variable	Characteristic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)		Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)		Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)		All Cohorts Secretor Negative (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx	x	xx	x	xx
	Female										
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx	x	xx	x	xx
	Hispanic or Latino										
	Not Reported										
	Unknown										
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	x	xx	x	xx
	Asian										
	Native Hawaiian or Other Pacific Islander										
	Black or African American										
	White										
	Multi-Racial										
	Unknown										
N = Number of participants enrolled.											

Table 14: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group, All Enrolled Participants

Variable	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)	All Participants (N=X)
Age (years)	Mean	xx	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx	xx
	Median	x	x	x	x	x
	Minimum	x	x	x	x	x
	Maximum	x	x	x	x	x

N = Number of participants enrolled.

14.1.3 Prior and Concurrent Medical Conditions

Table 15: Summary of Participants with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group

MedDRA System Organ Class	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)		Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)		Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)		All Cohorts Secretor Negative (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]										
[SOC 2]										

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

14.2 Illness, Infection, and Immunogenicity Data

14.2.1 Illness and Infection Data

Table 16: Occurrence of Norovirus-Associated Illness During the Inpatient Period by Treatment Group

Analysis Population	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive	Cohort 2 $3.5x10^4$ copies Secretor Positive	Cohort 3 $3.5x10^5$ copies Secretor Positive	All Cohorts Secretor Negative
Modified Intention-to-Treat	Illness, n[a]	n/N	n/N	n/N	n/N
	Illness Rate, %	xx	xx	xx	xx
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Per Protocol	Illness, n[a]	n/N	n/N	n/N	n/N
	Illness Rate, %	xx	xx	xx	xx
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x

Denominator used for percentages is the number of participants in the respective analysis population with illness data reported.
[a] Illness defined as diarrhea (≥3 loose or liquid stools (i.e., takes the shape of the container), or ≥300 gm of loose or liquid stools per 24 hrs), and/or vomiting during the inpatient period, in a participant with evidence of infection. The 24-hour period is defined as a study day from 00:00 to 23:59.

Table 17: Logistic Model-Predicted Probability of Norovirus-Associated Illness in Secretor Positive Participants

Analysis Population	Model Parameter	Parameter Estimate	Standard Error	Dose Corresponding to 50% of Participants with Illness
Modified Intention-to-Treat	Intercept (β_0)	x.xxx	x.xxx	xxxx
	Dose (β_1)	x.xxx	x.xxx	
Per Protocol	Intercept (β_0)	x.xxx	x.xxx	xxxx
	Dose (β_1)	x.xxx	x.xxx	

Table 18: Occurrence of Infection through Day 30 – mITT Population

Definition	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive	Cohort 2 $3.5x10^4$ copies Secretor Positive	Cohort 3 $3.5x10^5$ copies Secretor Positive	All Cohorts Secretor Negative
Detection of norovirus GII.4 in stool	Infection, n	n/N	n/N	n/N	n/N
	Infection Rate, %	xx	xx	xx	xx
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
≥4-fold rise in GII.4-specific antibody titers in serum IgG	Infection, n	n/N	n/N	n/N	n/N
	Infection Rate, %	xx	xx	xx	xx
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Detection of norovirus GII.4 in stool OR ≥4-fold rise in GII.4-specific antibody titers in serum IgG	Infection, n	n/N	n/N	n/N	n/N
	Infection Rate, %	xx	xx	xx	xx
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Denominator used for percentages is the number of participants in the mITT population with infection data reported.					

Tables with similar format:

Table 19: **Occurrence of Infection through Day 30 – PP Population**

Table 20: Overall Summary of Viral Secretion in PCR-Positive Stools - mITT Population

Parameter	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)
Peak Virus Concentration (GEC/g) [a]	n	x	x	x	x
	Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
	95% CI	x.xxx, x.xxx	x.xxx, x.xxx	x.xxx, x.xxx	x.xxx, x.xxx
	Median	x.xxx	x.xxx	x.xxx	x.xxx
	Min, Max	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Day of Peak Virus Concentration	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median (IQR)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Min, Max	x, x	x, x	x, x	x, x
Duration of Viral Secretion (Days)	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median (IQR)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Min, Max	x, x	x, x	x, x	x, x

N = Number of participants in the mITT population; n = Restricted to participants who were shedding on at least one day.

[a] Log_{10} transformation was used in calculating summary statistics

Tables with similar format:

Table 21: Overall Summary of Viral Secretion in PCR-Positive Stools – PP Population

Table 22: Distribution of Modified Vesikari Scale Parameters by Treatment Group, mITT Population

Parameter	Points	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)
Duration of Diarrhea	0	x (x%)	x (x%)	x (x%)	x (x%)
	1	x (x%)	x (x%)	x (x%)	x (x%)
	2	x (x%)	x (x%)	x (x%)	x (x%)
	3	x (x%)	x (x%)	x (x%)	x (x%)
Maximum number of diarrheal stools/24 hours	0				
	1				
	2				
	3				
Duration of Vomiting	0				
	1				
	2				
	3				
Maximum number of vomiting episodes/24 hours	0				
	1				
	2				
	3				
Fever (°C)	0				
	1				
	2				
	3				
Dehydration	0				
	2				

N = Number of participants in the mITT population.

Tables with similar format:

Table 23: Distribution of Modified Vesikari Scale Parameters by Treatment Group, PP Population

Table 24: Summary Statistics for Modified Vesikari Total Score by Treatment Group

Analysis Population	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive	Cohort 2 $3.5x10^4$ copies Secretor Positive	Cohort 3 $3.5x10^5$ copies Secretor Positive	All Cohorts Secretor Negative
Modified Intent-to-Treat	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
Per Protocol	n				
	Mean (SD)				
	Median				
	Min, Max				

Table 25: Duration (hours) of Vomiting and Diarrhea During the Inpatient Period by Treatment Group, mITT Population

Outcome	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)
Duration of Diarrhea	n	x	x	x	x
	Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
	Median	x.xxx	x.xxx	x.xxx	x.xxx
	Min, Max	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
Number of Episodes of Vomiting	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
Duration of Vomiting[a]	n	x	x	x	x
	Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
	Median	x.xxx	x.xxx	x.xxx	x.xxx
	Min, Max	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
Duration of Diarrhea and/or Vomiting	n	x	x	x	x
	Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
	Median	x.xxx	x.xxx	x.xxx	x.xxx
	Min, Max	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx

N = Number of participants in mITT population
[a] Duration of vomiting is calculated for participants with at least two episodes of vomiting in a study day.

Tables with similar format:

Table 26: Duration (hours) of Vomiting and Diarrhea During the Inpatient Period by Treatment Group, PP Population

14.2.3 Immunogenicity Data

Table 27: Serum GII.4-specific IgA Antibody GMT with 95% CIs by Time Point and Treatment Group, mITT Population

Time Point	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)
Pre-Challenge	n	x	x	x	x
	GMT	x.xx	x.xx	x.xx	x.xx
	95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Min, Max	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Day 15	n				
	GMT				
	95% CI				
	Min, Max				
Day 30	n				
	GMT				
	95% CI				
	Min, Max				
N=Number of participants in the mITT Population					

Tables with similar format:

Table 28: Serum GII.4-specific IgA Antibody GMT with 95% CIs by Time Point and Treatment Group, PP Population

Table 29: Serum GII.4-specific IgG Antibody GMT with 95% CIs by Time Point and Treatment Group, mITT Population

Table 30: Serum GII.4-specific IgG Antibody GMT with 95% CIs by Time Point and Treatment Group, PP Population

Table 31: Serum Blocking Antibody GMT with 95% CIs by Time Point and Treatment Group, mITT Population

Table 32: Serum Blocking Antibody GMT with 95% CIs by Time Point and Treatment Group, PP Population

Table 33: Serum GII.4-specific IgA Antibody GMFR and Seroresponse (4-Fold Rise) Results by Time Point and Treatment Group, mITT Population

Time Point	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)
Day 15	n	x	x	x	x
	GMFR	x.xx	x.xx	x.xx	x.xx
	95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	4-Fold Rise (%)	x	x	x	x
	95% CI	x, x	x, x	x, x	x, x
Day 30	n				
	GMFR				
	95% CI				
	4-Fold Rise (%)				
	95% CI				
N=Number of participants in the mITT Population					

Tables with similar format:

Table 34: Serum GII.4-specific IgA Antibody GMFR and Seroresponse (4-Fold Rise) Results by Time Point and Treatment Group, PP Population

Table 35: Serum GII.4-specific IgG Antibody GMFR and Seroresponse (4-Fold Rise) Results by Time Point and Treatment Group, mITT Population

Table 36: Serum GII.4-specific IgG Antibody GMFR and Seroresponse (4-Fold Rise) Results by Time Point and Treatment Group, PP Population

Table 37: Serum Blocking Antibody GMFR and Seroresponse (4-Fold Rise) Results by Time Point and Treatment Group, mITT Population

Table 38: Serum Blocking Antibody GMFR and Seroresponse (4-Fold Rise) Results by Time Point and Treatment Group, PP Population

Table 39: Association Between Baseline Antibody Titers and Infection, mITT population

Assay	Infection Status	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)
Serum IgG	Infected with illness	n	x	x	x	x
		GMT	x.xx	x.xx	x.xx	x.xx
		95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
	Infected without illness	n				
		GMT				
		95% CI				
	Uninfected	n				
		GMT				
		95% CI				
Serum IgA	Infected with illness	n				
		GMT				
		95% CI				
	Infected without illness	n				
		GMT				
		95% CI				
	Uninfected	n				
		GMT				
		95% CI				
Blocking Antibody	Infected with illness	n				
		GMT				
		95% CI				
	Infected without illness	n				
		GMT				
		95% CI				
	Uninfected	n				
		GMT				
		95% CI				

N = Number of participants in the mITT population; n = Number of participants with results reported

Tables with similar format:

Table 40: Association Between Baseline Antibody Titers and Infection, PP population

Table 41: Summary Statistics for GII.4-specific Memory B Cells by Time Point and Treatment Group, mITT Population

Time Point	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)
GII.4-specific IgG Secreting Memory B Cells per Total IgG Secreting Memory B Cells (%)					
Pre-Challenge	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
Day 30	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
Day 60	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
GII.4-specific IgA Secreting Memory B Cells per Total IgA Secreting Memory B Cells (%)					
Pre-Challenge	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
Day 30	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
Day 60	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
N=Number of participants in the mITT Population					

Tables with similar format:

Table 42: Summary Statistics for GII.4-specific Memory B Cells by Time Point and Treatment Group, PP Population

Table 43: Summary Statistics for IgA ASCs per 10^6 PBMCs by Time Point and Treatment Group, mITT Population

Time Point	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)
GII.4-specific IgA ASCs					
Pre-Challenge	n	x	x	x	x
	Mean (SD)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
Day 6	n	x	x	x	x
	Mean (SD)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
	Response[a] - % (95% CI)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Day 15	n				
	Mean (SD)				
	Median				
	Min, Max				
	Response[a] - % (95% CI)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Total IgA ASCs					
Pre-Challenge	n	x	x	x	x
	Mean (SD)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x
Day 6	n				
	Mean (SD)				
	Median				
	Min, Max				
Day 15	n				
	Mean (SD)				
	Median				
	Min, Max				
GII.4-specific IgA/Total IgA ASCs					
Pre-Challenge	n	x	x	x	x
	Mean (SD)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Median	x.x	x.x	x.x	x.x
	Min, Max	x, x	x, x	x, x	x, x

Time Point	Statistic	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)	Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)	Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)	All Cohorts Secretor Negative (N=X)
Day 6	n				
	Mean (SD)				
	Median				
	Min, Max				
Day 15	n				
	Mean (SD)				
	Median				
	Min, Max				

N=Number of participants in the mITT Population
[a] Response represents the percentage of participants with >0 GII.4-specific IgA ASCs.

Tables with similar format:

Table 44: Summary Statistics for IgA ASCs per 10^6 PBMCs by Time Point and Treatment Group, PP Population

Table 45: Summary Statistics for IgG ASCs per 10^6 PBMCs by Time Point and Treatment Group, mITT Population

Table 46: Summary Statistics for IgG ASCs per 10^6 PBMCs by Time Point and Treatment Group, PP Population

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 47: Overall Summary of Adverse Events

	Cohort 1 $3.5x10^3$ copies Secretor Positive (N = xx)		Cohort 2 $3.5x10^4$ copies Secretor Positive (N = xx)		Cohort 3 $3.5x10^5$ copies Secretor Positive (N = xx)		All Cohorts Secretor Negative (N = xx)		All Participants (N = xx)	
Participants[a] with	n	%	n	%	n	%	n	%	n	%
At least one systemic solicited adverse event through Day 10	x	x	x	x	x	x	x	x	x	x
At least one unsolicited adverse event	x	x	x	x	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x	x	x	x	x
At least one severe (Grade 3) unsolicited adverse event through Day 30	x	x	x	x	x	x	x	x	x	x
Related	x	x	x	x	x	x	x	x	x	x
Unrelated	x	x	x	x	x	x	x	x	x	x
At least one serious adverse event[b]	x	x	x	x	x	x	x	x	x	x
At least one related, serious adverse event	x	x	x	x	x	x	x	x	x	x
At least one adverse event leading to early termination[c]	x	x	x	x	x	x	x	x	x	x
At least one new onset chronic medical condition	x	x	x	x	x	x	x	x	x	x
At least one clinical safety laboratory adverse event	x	x	x	x	x	x	x	x	x	x

N = Number of participants in the Safety Population
[a] Participants are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Section 14.3.2.
[c] As reported on the Adverse Event eCRF.

Table 48: Adverse Events Occurring in 5% of Participants in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - Safety Population

[Implementation Note: this table is used to complete the "Other Adverse Event Template" for clinicaltrials.gov reporting (See slide 6 in https://prsinfo.clinicaltrials.gov/trainTrainer/Adverse-Events-Module.pdf). Threshold value may be 0% to 5% (default 5). This includes all adverse events collected (e.g., solicited, unsolicited, laboratory adverse events, etc.), regardless of relationship to study product.]

MedDRA Preferred Term	MedDRA System Organ Class	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)			Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)			Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)			All Cohorts Secretor Negative (N=X)			All Participants (N=X)		
		n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events																
All	All	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Etc.	Etc.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Other (Non-serious) Adverse Events																
All	All	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Etc	Etc	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

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

14.3.1.1 Solicited Adverse Events

Table 49: Number and Percentage of Participants Experiencing Solicited Events Post-Challenge with 95% Confidence Intervals by Symptom and Treatment Group

Symptom	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)			Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)			Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)			All Cohorts Secretor Negative (N=X)		
	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
Fever (oral temperature)												
Headache												
Nausea												
Abdominal cramps, discomfort, pain												
Abdominal gurgling												
Abdominal bloating												
Myalgia												
Malaise, fatigue												
Anorexia, loss of appetite												
Chills												
N = Number of participants in the Safety Population												

Table 50: Number and Percentage of Participants Experiencing Solicited Events Post-Challenge by Symptom, Maximum Severity, and Treatment Group

Symptom	Severity	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)			Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)			Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)			All Cohorts Secretor Negative (N=X)		
		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
	Mild												
	Moderate												
	Severe												
Fever (oral temperature)	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
	Mild												
	Moderate												
	Severe												
Headache	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
	Mild												
	Moderate												
	Severe												
Nausea	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
	Mild												
	Moderate												
	Severe												
Abdominal cramps, discomfort, pain	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
	Mild												
	Moderate												
	Severe												
Abdominal gurgling	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
	Mild												
	Moderate												

Symptom	Severity	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)			Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)			Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)			All Cohorts Secretor Negative (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
	Severe												
Abdominal bloating	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
	Mild												
	Moderate												
	Severe												
Myalgia	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
	Mild												
	Moderate												
	Severe												
Malaise, fatigue	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
	Mild												
	Moderate												
	Severe												
Anorexia, loss of appetite	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
	Mild												
	Moderate												
	Severe												
Chills	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
	Mild												
	Moderate												
	Severe												

Note: N = Number of participants in the Safety Population. Severity is the maximum severity reported over all solicited symptoms post dosing for each participant.

Table 51: Number and Percentage of Participants Experiencing Solicited Events Post-Challenge by Symptom, Maximum Severity (Dichotomized), and Treatment Group

Symptom	Severity	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)			Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)			Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)			All Cohorts Secretor Negative (N=X)		
		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
	Mild, Moderate, or Severe												
Fever (oral temperature)	None												
	Mild, Moderate, or Severe												
Headache	None												
	Mild, Moderate, or Severe												
Nausea	None												
	Mild, Moderate, or Severe												
Abdominal cramps, discomfort, pain	None												
	Mild, Moderate, or Severe												
Abdominal gurgling	None												
	Mild, Moderate, or Severe												
Abdominal bloating	None												
	Mild, Moderate, or Severe												
Myalgia	None												
	Mild, Moderate, or Severe												
Malaise, fatigue	None												
	Mild, Moderate, or Severe												
Anorexia, loss of appetite	None												
	Mild, Moderate, or Severe												
Chills	None												
	Mild, Moderate, or Severe												

Note: N = Number of participants in the Safety Population. Severity is the maximum severity reported over all solicited symptoms post challenge for each participant.

Table 52: Logistic Regression Model to Examine the Relationship Between Any Systemic Event Post-Challenge and Treatment Group

Model Parameter	Parameter Category	Parameter Estimate	Standard Error	Odds Ratio	95% CI
Intercept	N/A	xxx.x	xxx.x	-	-
Treatment Group	Cohort 1 $3.5x10^3$ copies Secretor Positive	xxx.x	xxx.x	xx.x	xx.x-xx.x
	Cohort 2 $3.5x10^4$ copies Secretor Positive	xxx.x	xxx.x	xx.x	xx.x-xx.x
	Cohort 3 $3.5x10^5$ copies Secretor Positive	xxx.x	xxx.x	xx.x	xx.x-xx.x
	All Cohorts Secretor Negative	-	-	-	-

N = Number of participants in the Safety population.

Table 53: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Day Post-Challenge, and Treatment Group - Cohort 1, $3.5x10^3$ copies, Secretor Positive

Symptom	Severity	Pre-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9		Day 10		Day 10+	
		n	%	n	%	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	x	xx	x	xx
	Mild																								
	Moderate																								
	Severe																								
	Not Reported																								
Fever (oral temperature)	None																								
	Mild																								
	Moderate																								
	Severe																								
	Not Reported																								
Headache	None																								
	Mild																								
	Moderate																								
	Severe																								
	Not Reported																								
Nausea	None																								
	Mild																								
	Moderate																								
	Severe																								
	Not Reported																								
Abdominal cramps, discomfort, pain	None																								
	Mild																								
	Moderate																								

Symptom	Severity	Pre-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9		Day 10		Day 10+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Severe																								
	Not Reported																								
Abdominal gurgling	None																								
	Mild																								
	Moderate																								
	Severe																								
	Not Reported																								
Abdominal bloating	None																								
	Mild																								
	Moderate																								
	Severe																								
	Not Reported																								
Myalgia	None																								
	Mild																								
	Moderate																								
	Severe																								
	Not Reported																								
Malaise, fatigue	None																								
	Mild																								
	Moderate																								
	Severe																								
	Not Reported																								
Anorexia, loss of appetite	None																								
	Mild																								
	Moderate																								

Symptom	Severity	Pre-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9		Day 10		Day 10+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Severe																								
	Not Reported																								
Chills	None																								
	Mild																								
	Moderate																								
	Severe																								
	Not Reported																								
Note: N = Number of participants in the Safety Population. Severity is the maximum severity reported post challenge for each participant for each day.																									

Tables with similar format:

Table 54: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Day Post-Challenge, and Treatment Group - Cohort 2, $3.5x10^4$ copies, Secretor Positive

Table 55: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Day Post-Challenge, and Treatment Group - Cohort 3, $3.5x10^5$ copies, Secretor Positive

Table 56: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Day Post-Challenge, and Treatment Group – All Cohorts, Secretor Negative

14.3.1.2 Unsolicited Adverse Events

Table 57: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Dose Number, and Treatment Group – Cohort 1, 3.5x10^3 copies, Secretor Positive

		Day 1-10 Post-Challenge (N=X)				Day 11-30 Post-Challenge (N=X)				Day 31-180 Post-Challenge (N=X)				Any Time Post-Challenge (N=X)			
MedDRA System Organ Class	**MedDRA Preferred Term**	**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
[SOC 1]	Any PT																
	[PT 1]																
	[PT 2]																
[SOC 2]	Any PT																
	[PT 1]																
	[PT 2]																

Note: N = number of participants in the Safety Population who received the specified dose. This table presents number and percentage of participants. A participant is only counted once per PT/time point.

Tables with similar format:

Table 58: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Dose Number, and Treatment Group – Cohort 2, 3.5x10^4 copies, Secretor Positive

Table 59: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Dose Number, and Treatment Group – Cohort 3, 3.5x10^5 copies, Secretor Positive

Table 60: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Dose Number, and Treatment Group – All Cohorts, Secretor Negative

Table 61: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group – Cohort 1, $3.5x10^3$ copies, Secretor Positive

MedDRA System Organ Class	MedDRA Preferred Term	Severity	Cohort 1 $3.5x10^3$ copies Secretor Positive (N = X)					
			Related		Not Related		Total	
			n	%	n	%	n	%
Any SOC	Any PT	Any Severity	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx
[SOC 1]	Any PT	Any Severity	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx
	[PT 1]	Any Severity	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx

N = Number of participants in the safety population.

Tables with similar format:

Table 62: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group – Cohort 2, $3.5x10^4$ copies, Secretor Positive

Table 63: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group – Cohort 3, $3.5x10^5$ copies, Secretor Positive

Table 64: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group – All Cohorts, Secretor Negative

Table 65: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group – All Participants

Table 66: Related Unsolicited Adverse Events Within 10 Days Post-Challenge by MedDRA System Organ Class and Preferred Term, and Treatment Group

		Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)			Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)			Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)			All Cohorts Secretor Negative (N=X)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**
Any SOC	Any PT	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 participants in the Safety Population. This table presents number and percentage of participants. For each time point, a participant is only counted once per PT.													

Table 67: Severe Unsolicited Adverse Events through Day 30 Post-Challenge by MedDRA System Organ Class and Preferred Term, and Treatment Group

[Implementation Note: If there are no Grade 3 (Severe) unsolicited AEs reported in any treatment group during this timeframe, then the table will only consist of the first row (Any SOC, Any PT) with n and % equal to zero and appropriate 95% CIs.]

		Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)			Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)			Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)			All Cohorts Secretor Negative (N=X)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any SOC	Any PT	x	xx	xx.x, xx.x	x	xx	xx.x, xx.x	x	xx	xx.x, xx.x	x	xx	xx.x, xx.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of participants in the Safety Population. This table presents number and percentage of participants. For each time point, a participant is only counted once per PT.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 68: Listing of Serious Adverse Events

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" for the "Duration". If more than one reason is selected for the reason reported as an SAE, list all reasons in the column, separated by a comma. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. If there are no comments for an event, populate 'Comments' row with 'None'. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Participant ID and No. of Days Post-Challenge.]

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

Table 69: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. If there are no comments for an event, populate 'Comments' row with 'None'. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Participant ID and No. of Days Post-Challenge.]

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

Table 70: Listing of New Onset Chronic Medical Conditions

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. If there are no comments for an event, populate 'Comments' row with 'None'. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Participant ID and AE Number]

Adverse Event	No. of Days Post-Challenge (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternate Etiology	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Participant ID: , Treatment Group: , AE Number:								
Comments:								
Participant 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 Participant)

Table 71: Listing of Abnormal Laboratory Results - Chemistry

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing should include all chemistry results for any participant that had at least one abnormal chemistry laboratory result. A complete listing of all laboratory results is included in the listings document. In the Laboratory Parameter column, indicate the units after the parameter, e.g., Hemoglobin (g/dL). This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 16.2 (mild). In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order should be USUBJID, Laboratory Parameter, Actual Study Day]

Participant 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	Participant Discontinued Due to Result?

Table 72: Listing of Abnormal Laboratory Results - Hematology

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing should include all hematology results for any participant that had at least one abnormal hematology laboratory result. A complete listing of all laboratory results is included in the listings document. In the Laboratory Parameter column, indicate the units after the parameter, e.g., Hemoglobin (g/dL).This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 16.2 (mild).In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order should be USUBJID, Laboratory Parameter, Actual Study Day]

Participant 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	Participant Discontinued Due to Result?

Table 73: Listing of Abnormal Laboratory Results - Urinalysis

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. This listing should include all urinalysis results for any participant that had at least one abnormal urinalysis laboratory result. A complete listing of all laboratory results is included in the listings document. In the Laboratory Parameter column, indicate the units after the parameter, e.g., Hemoglobin (g/dL).This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 16.2 (mild).In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order should be USUBJID, Laboratory Parameter, Actual Study Day]

Participant 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	Participant Discontinued Due to Result?

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 74: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Chemistry Parameter

[Implementation Note: This table will only be generated if at least one participant has safety chemistry labs drawn post-challenge administration.]

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	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive											
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive											
	All Cohorts – Secretor Negative											
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 5	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											

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

Table 75: Laboratory Results by Parameter Time Point, and Treatment Group – ALT

[Implementation Note: This table will only be generated if at least one participant has safety chemistry labs drawn post-challenge administration.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive											
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive											
	All Cohorts – Secretor Negative											
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 5	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											

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

Tables with similar format:

Table 76: Laboratory Results by Parameter Time Point, and Treatment Group – Total Bilirubin

[Implementation Note: This table will only be generated if at least one participant has safety chemistry labs drawn post-challenge administration.]

Table 77: Laboratory Results by Parameter Time Point, and Treatment Group – Creatinine

[Implementation Note: This table will only be generated if at least one participant has safety chemistry labs drawn post-challenge administration.]

Table 78: Laboratory Results by Parameter Time Point, and Treatment Group – Potassium

[Implementation Note: This table will only be generated if at least one participant has safety chemistry labs drawn post-challenge administration.]

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	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive																	
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive																	
	All Cohorts – Secretor Negative																	
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 5	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	

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

Tables with similar format:

Table 79: Laboratory Results by Parameter Time Point, and Treatment Group – Sodium

[Implementation Note: This table will only be generated if at least one participant has safety chemistry labs drawn post-challenge administration.]

Table 80: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – ALT (U/L)

[Implementation note: For Days 1-5, only time points with laboratory results available will be presented in this table.]

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive					
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive					
	All Cohorts – Secretor Negative					
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					
Day 1, Change from Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					
…	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					
Day 5	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					
Day 5, Change from Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					

Note: N = Number of participants in the Safety Population with non-missing data for the given time point.

Tables with similar format:

Table 81: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Total Bilirubin (mg/dL)

[Implementation note: For Days 1-5, only time points with laboratory results available will be presented in this table.]

Table 82: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Creatinine (mg/dL)

[Implementation note: For Days 1-5, only time points with laboratory results available will be presented in this table.]

Table 83: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Potassium (mmol/L)

[Implementation note: For Days 1-5, only time points with laboratory results available will be presented in this table.]

Table 84: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Sodium (mmol/L)

[Implementation note: For Days 1-5, only time points with laboratory results available will be presented in this table.]

14.3.5.2 Hematology Results

Table 85: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Hematology Parameter

[Implementation Note: This table will only be generated if at least one participant has safety hematology labs drawn post-challenge administration.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive											
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive											
	All Cohorts – Secretor Negative											
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 5	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											

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

Table 86: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – White Blood Cells

[Implementation Note: This table will only be generated if at least one participant has safety hematology labs drawn post-challenge administration.]

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	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive																	
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive																	
	All Cohorts – Secretor Negative																	
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 5	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	

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

Table 87: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Absolute Neutrophil Count

[Implementation Note: This table will only be generated if at least one participant has safety hematology labs drawn post-challenge administration.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive											
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive											
	All Cohorts – Secretor Negative											
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 5	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											

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

Tables with similar format:

Table 88: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Hemoglobin

[Implementation Note: This table will only be generated if at least one participant has safety hematology labs drawn post-challenge administration.]

Table 89: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Platelet Count

[Implementation Note: This table will only be generated if at least one participant has safety hematology labs drawn post-challenge administration.]

Table 90: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – White Blood Cells (10^9/L)

[Implementation note: For Days 1-5, only time points with laboratory results available will be presented in this table.]

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive					
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive					
	All Cohorts – Secretor Negative					
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					
Day 1, Change from Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					
…	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					
Day 5	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					
Day 5, Change from Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive					
	…					

Note: N = Number of participants in the Safety Population with non-missing data for the given time point.

Tables with similar format:

Table 91: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Absolute Neutrophil Count (10^9/L)

[Implementation note: For Days 1-5, only time points with laboratory results available will be presented in this table.]

Table 92: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hemoglobin (g/dL)

[Implementation note: For Days 1-5, only time points with laboratory results available will be presented in this table.]

Table 93: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Platelet Count (10^9/L)

[Implementation note: For Days 1-5, only time points with laboratory results available will be presented in this table.]

14.3.5.3 Urinalysis Results

Table 94: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Urine Protein

[Implementation Note: This table will only be generated if at least one participant has safety chemistry labs drawn post-challenge administration.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive											
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive											
	All Cohorts – Secretor Negative											
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 5	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											

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

14.3.6 Displays of Vital Signs

Table 95: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Any Assessment

[Implementation note: For post-baseline time points, only those with vital signs results available will be presented in this table.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive											
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive											
	All Cohorts – Secretor Negative											
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
…	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											

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

Table 96: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group –Systolic Blood Pressure

[Implementation note: For post-baseline time points, only those with systolic blood pressure results available will be presented in this table.]

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	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive																	
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive																	
	All Cohorts – Secretor Negative																	
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
…	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	

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

Table 97: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Diastolic Blood Pressure

[Implementation note: For post-baseline time points, only those with vital signs results available will be presented in this table.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive											
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive											
	All Cohorts – Secretor Negative											
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
…	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											

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

Table 98: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Pulse

[Implementation note: For post-baseline time points, only those with systolic blood pressure results available will be presented in this table.]

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	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive																	
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive																	
	All Cohorts – Secretor Negative																	
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
…	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive																	
	…																	

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

Table 99: Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group – Oral Temperature

[Implementation note: For post-baseline time points, only those with vital signs results available will be presented in this table.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Cohort 2 – $3.5x10^4$ copies, Secretor Positive											
	Cohort 3 – $3.5x10^5$ copies, Secretor Positive											
	All Cohorts – Secretor Negative											
Day 1	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 2	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 3	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Day 4	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
…	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											
Max Severity Post Baseline	Cohort 1 – $3.5x10^3$ copies, Secretor Positive											
	…											

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

14.4 Summary of Concomitant Medications

Table 100: Number and Percentage of Participants 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	Cohort 1 $3.5x10^3$ copies Secretor Positive (N=X)		Cohort 2 $3.5x10^4$ copies Secretor Positive (N=X)		Cohort 3 $3.5x10^5$ copies Secretor Positive (N=X)		All Cohorts Secretor Negative (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	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]	Any [ATC1-2]										
	[ATC 2 - 1]										
	[ATC 2 - 2]										
	[ATC 2 - 3]										

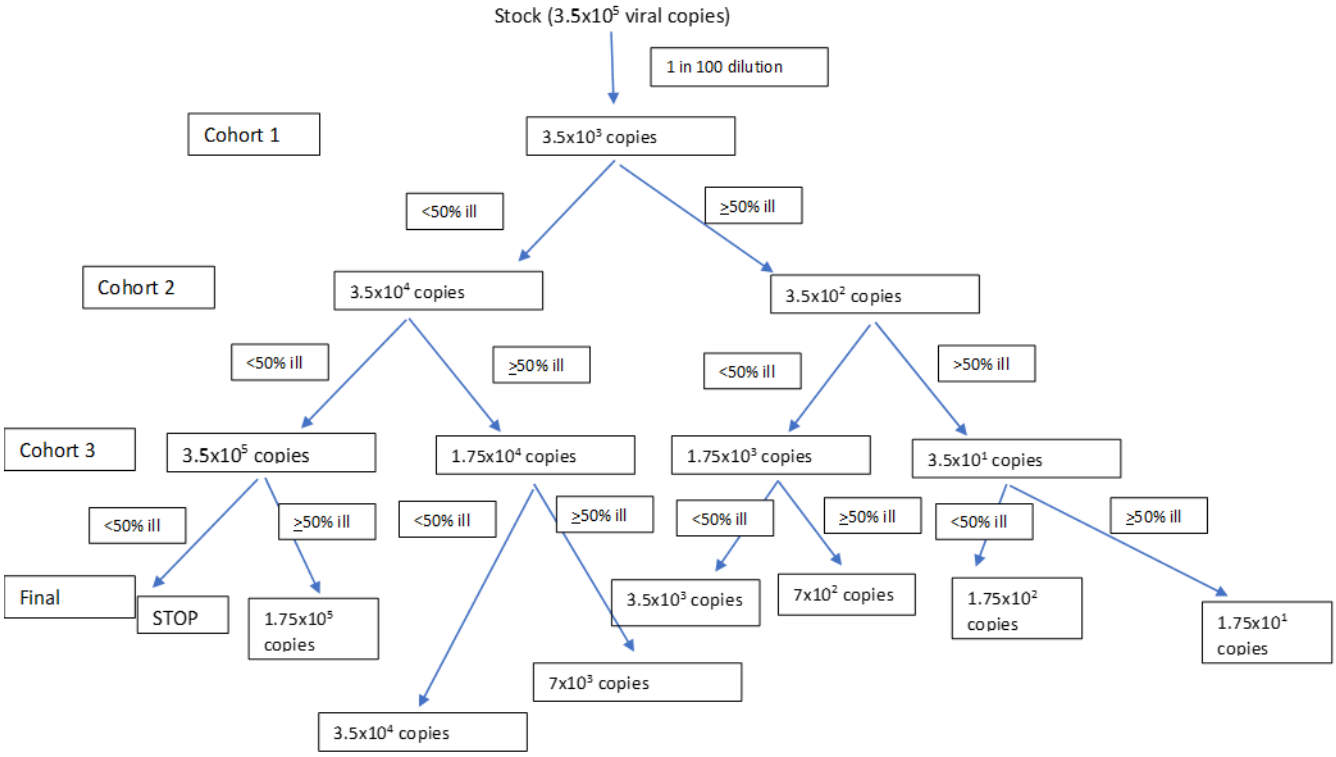
N = Number of participants in the Safety Population. n=Number of participants reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

9.1 Overall Study Design and Plan Description

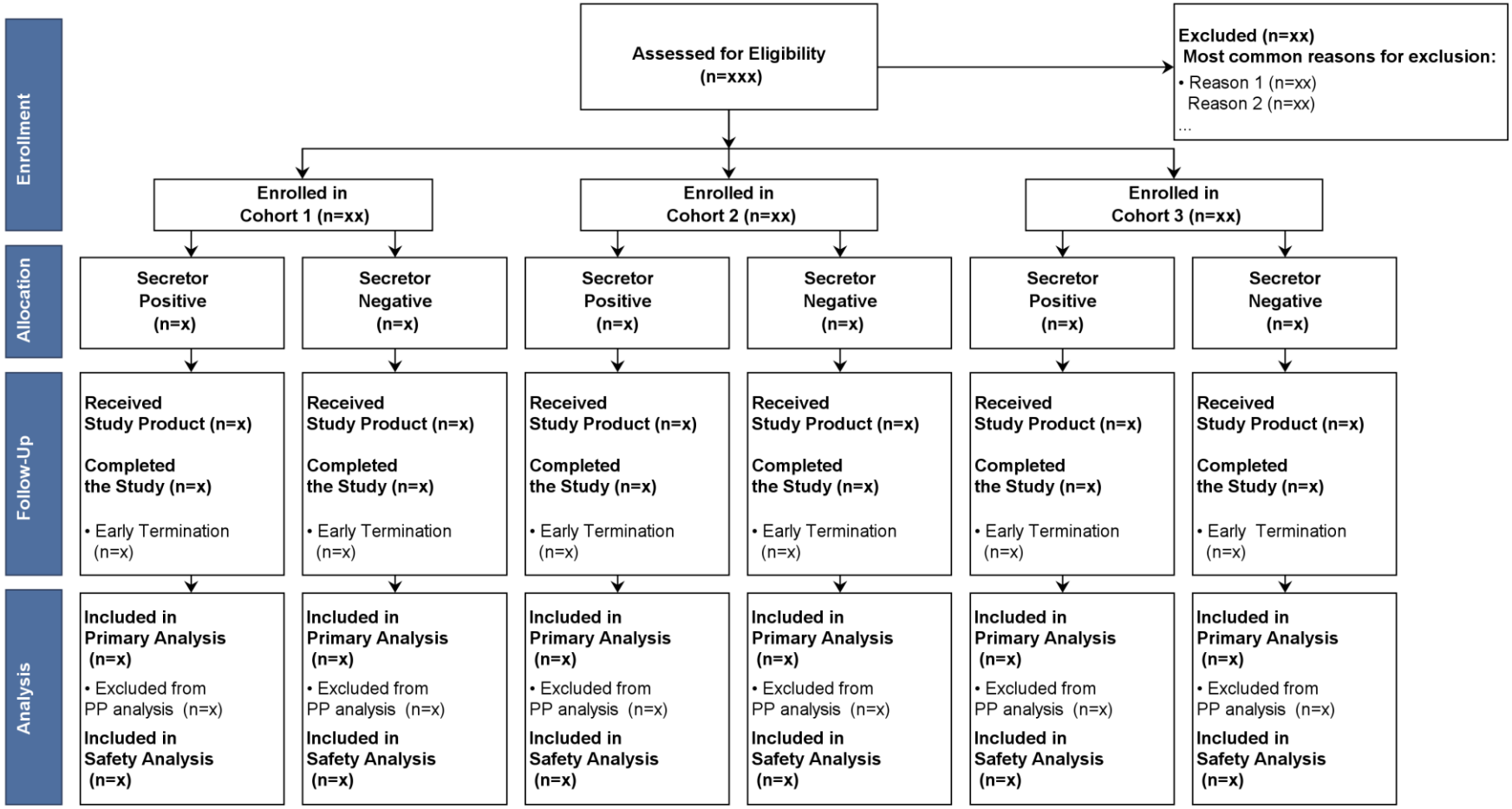
Figure 1: Study Design



"Final" is the dose to be used in the future and not within this protocol.

10.1 Disposition of Participants

Figure 2: CONSORT Flow Diagram



14.2.2 Illness and Infection Response Figures

Figure 3: Distribution of Modified Vesikari Scores by Treatment Group, mITT Population

[Implementation note: Box-plots will be generated with Treatment Groups on the x-axis and Modified Vesikari Score on the y-axis.]

Figure with similar format:

Figure 4: Distribution of Modified Vesikari Scores by Treatment Group, PP Population

Figure 5: Estimated Population Regression Model for Virus Shedding Over Time, mITT Population

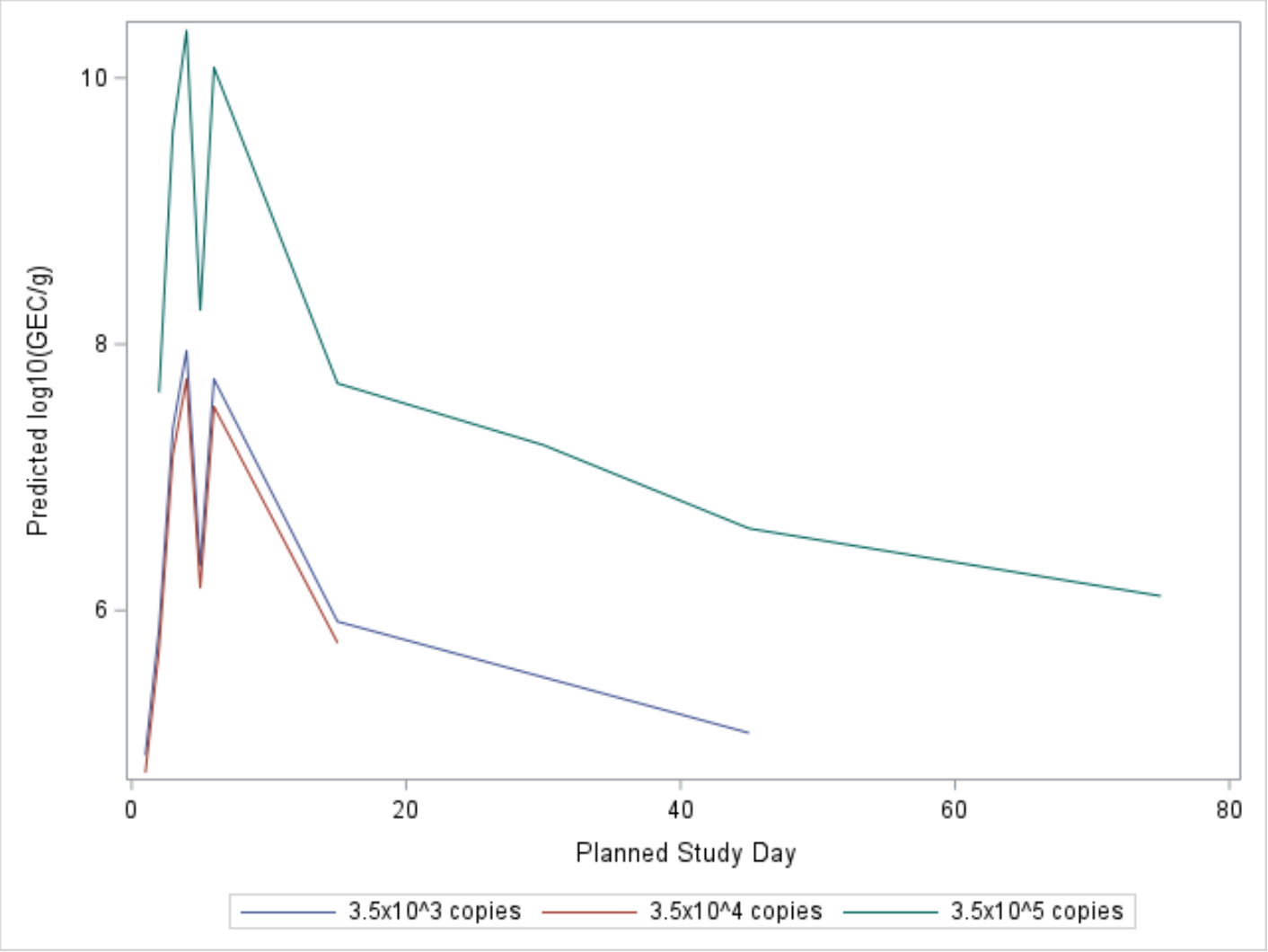


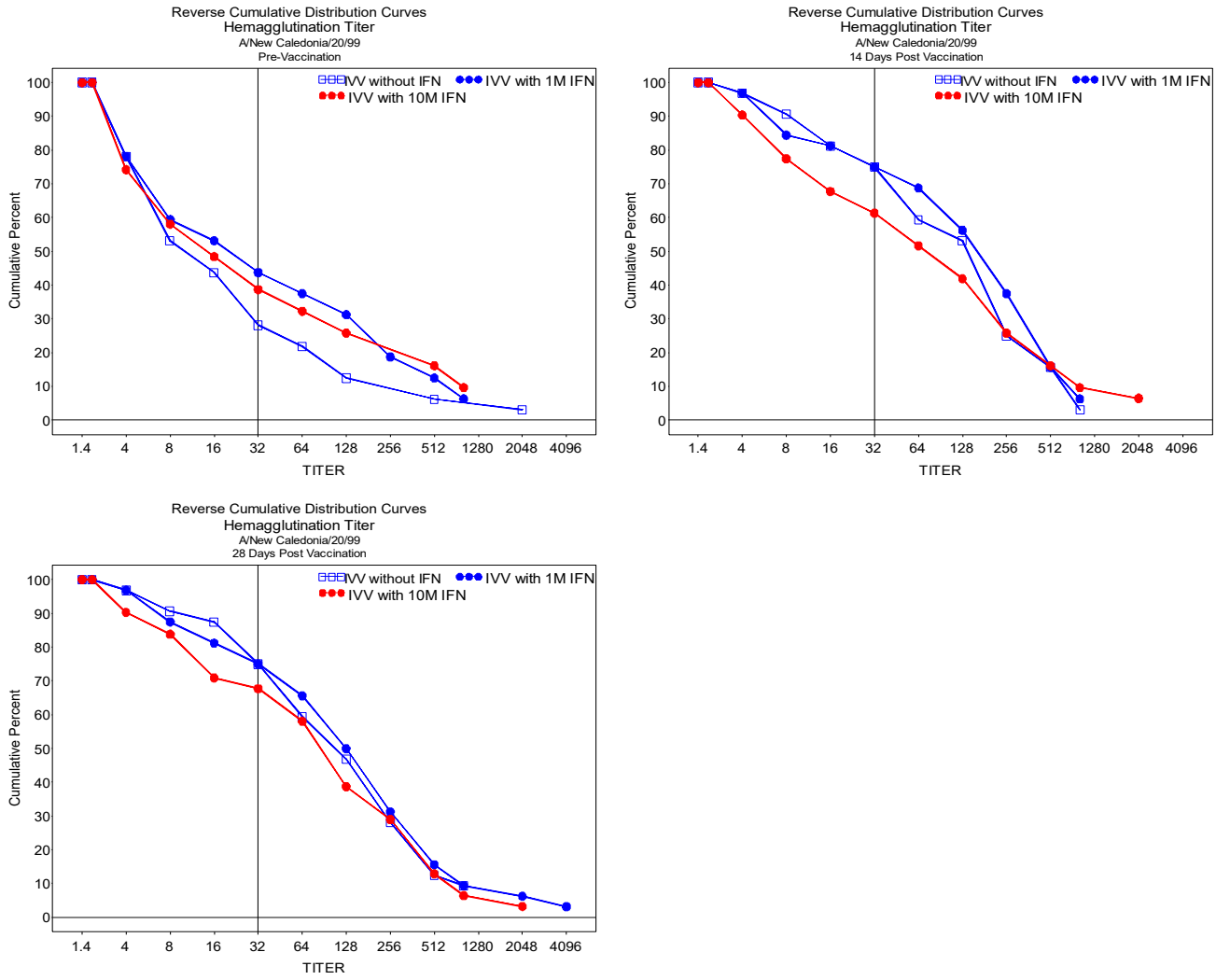
Figure with similar format:

Figure 6: Estimated Population Regression Model for Virus Shedding Over Time, PP Population

14.2.4 Immunogenicity Response Figures by Measure and Time Point

Figure 7: Reverse Cumulative Distribution of GII.4-specific Serum IgA by Time Point and Treatment Group, mITT Population

[Implementation note: The graphs below are examples and will be adapted to include separate lines to present all Study Groups for DMID 17-0102. There will be three panels for Pre-Challenge, Day 15, and Day 30.]



Figures with similar format:

Figure 8: Reverse Cumulative Distribution of GII.4-specific Serum IgA by Time Point and Treatment Group, PP Population

Figure 9: Reverse Cumulative Distribution of GII.4-specific Serum IgG by Time Point and Treatment Group, mITT Population

Figure 10: Reverse Cumulative Distribution of GII.4-specific Serum IgG by Time Point and Treatment Group, PP Population

Figure 11: Reverse Cumulative Distribution of Serum Blockade by Time Point and Treatment Group, mITT Population

Figure 12: Reverse Cumulative Distribution of Serum Blockade by Time Point and Treatment Group, PP Population

Figure 13: Reverse Cumulative Distribution of Pre-Challenge Antibody Responses by Infection Status, mITT Population

[Implementation note: The graphs below are examples and will be adapted to include separate lines for each infection status (Infected with Illness, Infected without Illness, Uninfected) and separate panels for NoV GII.4 Serum IgG, NoV GII.4 Serum IgA, Blocking Antibody]

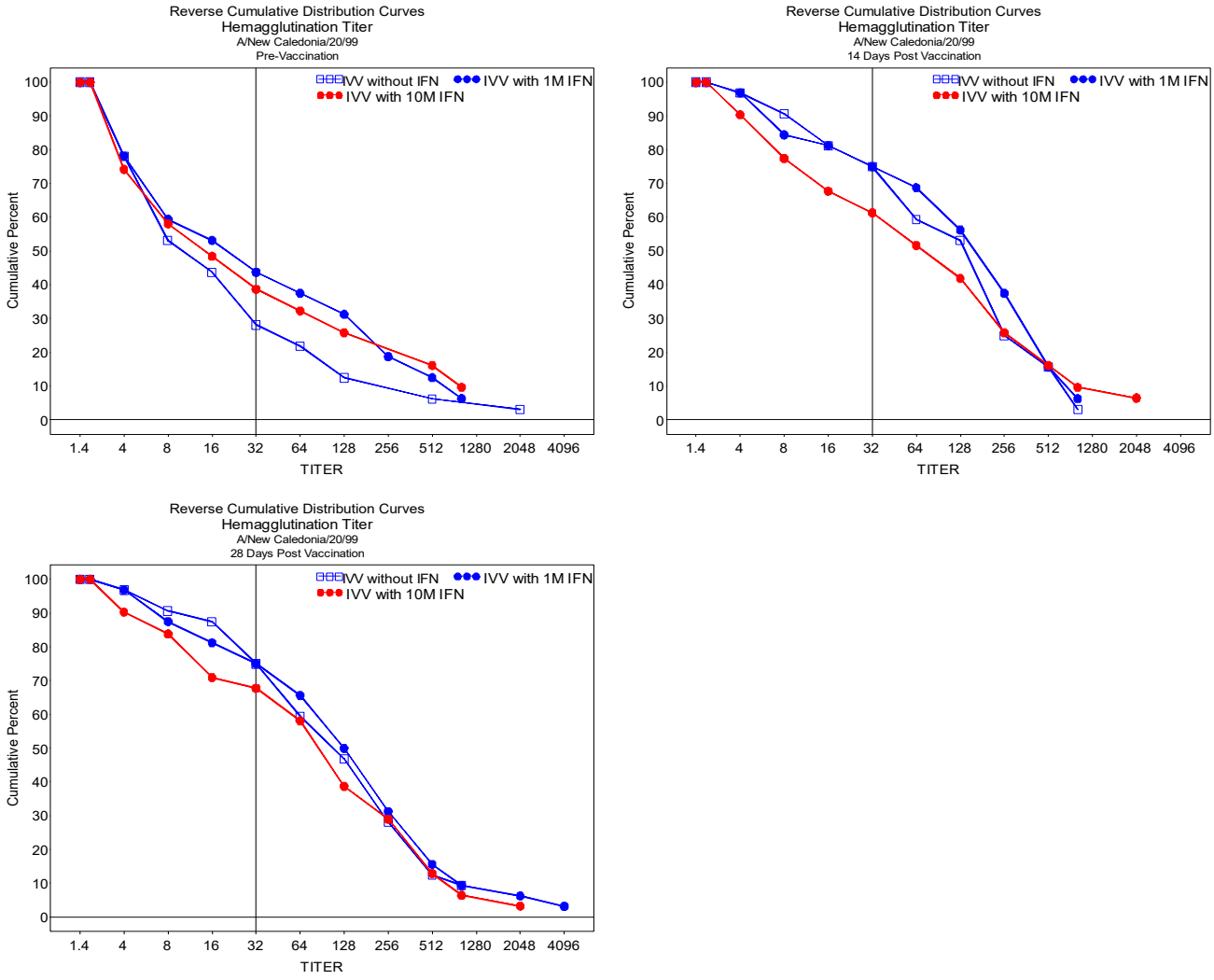


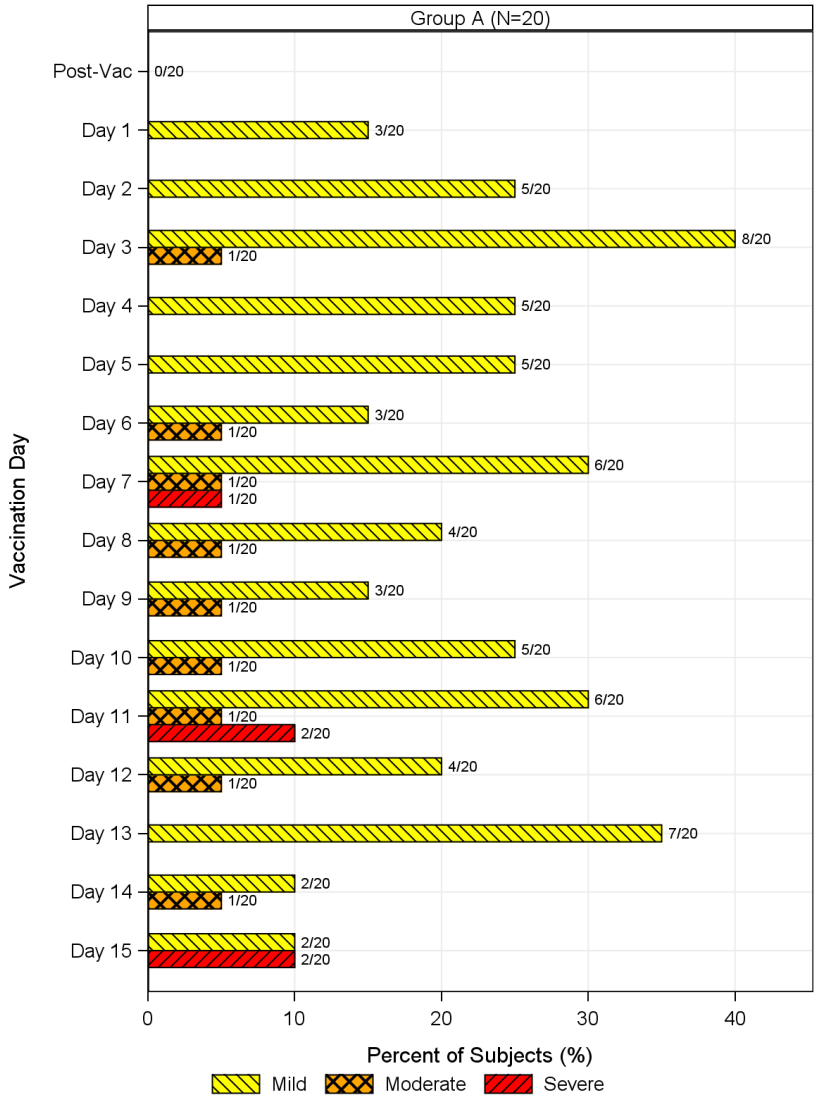
Figure with similar format:

Figure 14: Reverse Cumulative Distribution of Pre-Challenge Antibody Responses by Infection Status, PP Population

14.3.1.1 Solicited Adverse Events

Figure 15: Maximum Severity of Solicited Systemic Symptoms per Participant by Day Post Challenge – Cohort 1, 3.5x10^3 copies, Secretor Positive

[Implementation Note: The figure below is an example only. The y-axis will be labeled "Post Challenge Day". The x-axis will indicate "Percentage of Participants (%)".]



Figures with similar format:

Figure 16: Maximum Severity of Solicited Systemic Symptoms per Participant by Day Post Challenge – Cohort 2, 3.5x10^4 copies, Secretor Positive

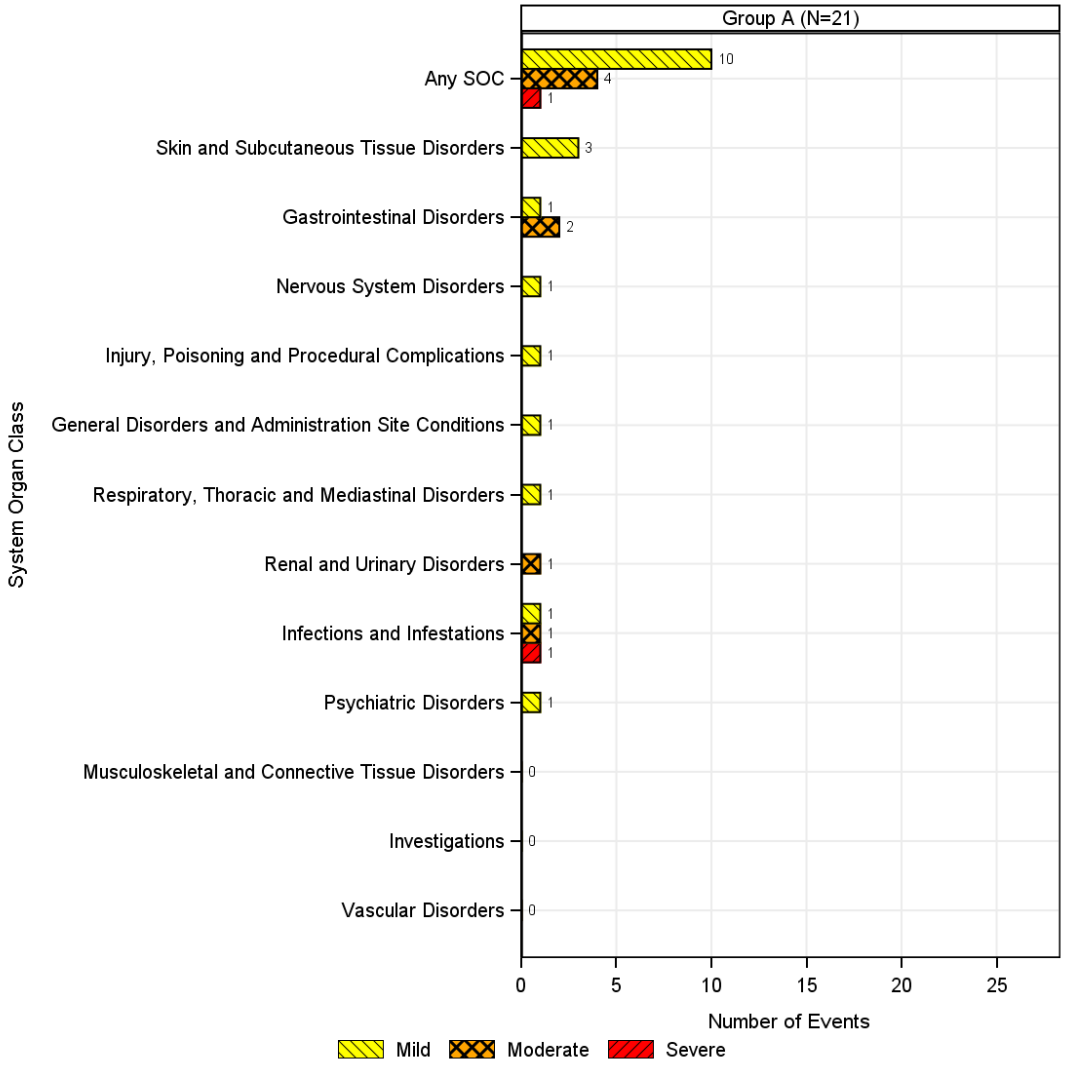
Figure 17: Maximum Severity of Solicited Systemic Symptoms per Participant by Day Post Challenge – Cohort 3, 3.5x10^5 copies, Secretor Positive

Figure 18: Maximum Severity of Solicited Systemic Symptoms per Participant by Day Post Challenge – All Cohorts, Secretor Negative

14.3.1.2 Unsolicited Adverse Events

Figure 19: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity – Cohort 1, 3.5x10^3 copies, Secretor Positive

[Implementation Note: The figure below is an example only. This figure includes serious and non-serious unsolicited adverse events deemed related to study product. The SOCs will be sorted in descending frequency; e.g., for this figure, "Gastrointestinal Disorders" should be listed first.]



Figures with similar format:

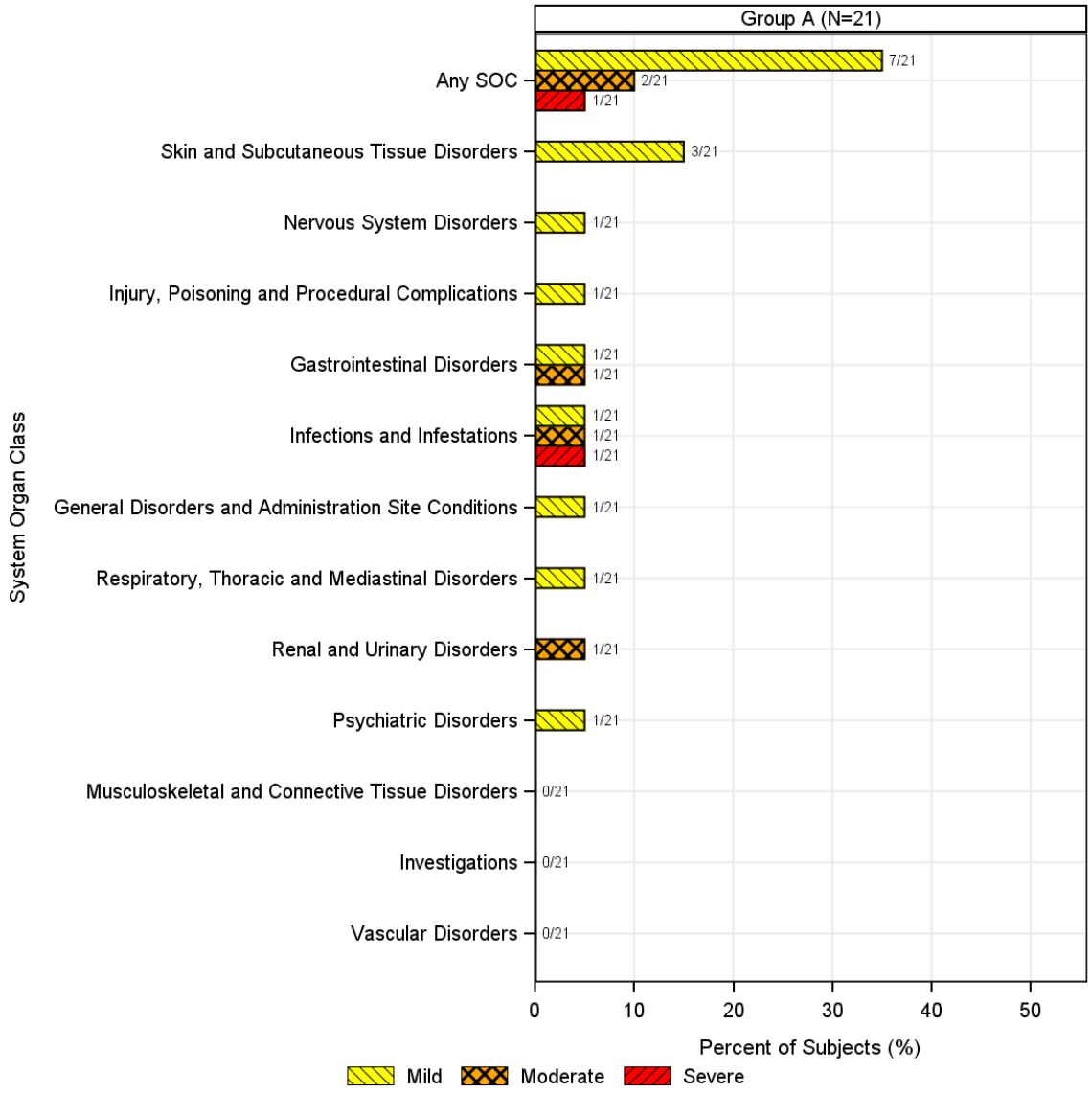
Figure 20: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity – Cohort 2, 3.5x10^4 copies, Secretor Positive

Figure 21: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity – Cohort 3, 3.5x10^5 copies, Secretor Positive

Figure 22: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity – All Cohorts, Secretor Negative

Figure 23: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity – Cohort 1, 3.5x10^3 copies, Secretor Positive

[Implementation Note: The figure below is an example only. This figure includes serious and non-serious unsolicited adverse events deemed related to study product. The SOCs will be sorted in descending incidence; e.g., for this figure, "Infections and infestations" should be listed first.]



Figures with similar format:

Figure 24: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity – Cohort 2, 3.5x10^4 copies, Secretor Positive

Figure 25: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity – Cohort 3, 3.5x10^5 copies, Secretor Positive

Figure 26: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity – All Cohorts, Secretor Negative

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: **16.1.6: Listing of Participants Receiving Investigational Product**

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

16.2 Database Listings by Participant

16.2.1 Discontinued Participants

Listing 2: 16.2.1: Early Terminations

[Implementation Note: In the "Reason for Early Termination" column, concatenate any "specify" fields, including AE number and DV number. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID.]

Treatment Group	Participant ID	Reason for Early Termination	Study Day

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Participant-Specific Protocol Deviations

[Implementation Note: In the "Deviation" column, concatenate any and all "specify" fields (including visit number, etc.). If "Reason for Deviation" is "Other," concatenate "specify" field, separate by a colon, e.g., "Other: Participant refusal." In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, DV Number.]

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

Listing 4: 16.2.2.2: Non-Participant-Specific Protocol Deviations

[Implementation Note: In the "Deviation" column, concatenate any and all "specify" fields (including visit number, etc.). If "Reason for Deviation" is "Other," concatenate "specify" field, separate by a colon, e.g., "Other: Participant refusal." Sort order: Site, Start Date.]

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

16.2.3 Participants Excluded from the Efficacy Analysis

Listing 5: 16.2.3: Participants Excluded from Analysis Populations

[Implementation Note: In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: Treatment Group, Participant ID.]

Treatment Group	Participant ID	Analyses in which Participant is Included	Analyses from which Participant is Excluded	Results Available?	Reason Participant Excluded
		[e.g., Safety,m ITT, 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 6: 16.2.4.1: Demographic Data

[Implementation Note: If a participant is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)."In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: Treatment Group, Participant ID.]

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

Listing 7: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

[Implementation Note: "Condition Start Day" and "Condition End Day" are relative to enrollment (which is Day 1, day before enrollment is Day -1). Rather than use exact study days, categorize as follows:>5 years prior to enrollment, 1-5 years prior to enrollment, 1-12 months prior to enrollment, Within 1 month of enrollment, During study. If ongoing, display "Ongoing" in the "Condition End Day" column. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, MH Number.]

Treatment Group	Participant 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)

Listing 8: 16.2.5: Compliance and/or Drug Concentration Data

				Actual Dosage Administered	
Cohort	**Vial #**	**Dilution**	**If diluted, what dilution?**	**Cycle Threshold**	**Genome Copies per Milliliter**
Cohort 1 - $3.5x10^3$ copies	1				
Cohort 1 - $3.5x10^3$ copies	2				
Cohort 2 – $3.5x10^4$ copies	1				
Cohort 2 – $3.5x10^4$ copies	2				
Cohort 3 – $3.5x10^5$ copies	1				
Cohort 3 – $3.5x10^5$ copies	2				

16.2.6 Individual Infection and Immunogenicity Response Data

Listing 9: 16.2.6.1: Individual qRT-PCR Viral Load Data

[Implementation Note: In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Participant ID, Actual Study Day.]

Treatment Group	Participant ID	Planned Time Point	Actual Study Day	Qualitative Result	Cycle Threshold	Genome Copies per Gram of Stool

Listing 10: 16.2.6.2: Individual Serum GII.4-Specific Antibody Data

[Implementation Note: In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Participant ID, Actual Study Day.]

Treatment Group	Participant ID	Planned Time Point	Actual Study Day	IgA Titer	IgA Fold-Rise	IgG Titer	IgG Fold-Rise	Blocking Titer	Blocking Fold-Rise

Listing 11: 16.2.6.2: Individual Memory B Cells Data

[Implementation Note: In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Participant ID, Actual Study Day.]

Treatment Group	Participant ID	Planned Time Point	Actual Study Day	GII.4-specific IgG secreting Memory B Cells over Total IgG secreting Memory B Cells (%)	GII.4-specific IgA secreting Memory B Cells over Total IgA secreting Memory B Cells (%)

Listing 12: 16.2.6.2: Individual ASC Data

[Implementation Note: In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Participant ID, Actual Study Day.]

Treatment Group	Participant ID	Planned Time Point	Actual Study Day	GII.4-specific IgG ASCs	Total IgG ASCs	GII.4-specific IgG /Total IgG ASCs	GII.4-specific IgA ASCs	Total IgA ASCs	GII.4-specific IgA /Total IgA ASCs

16.2.7 Adverse Events

Listing 13: 16.2.7.1: Solicited Events – Systemic Symptoms

[Implementation Note: This listing is not color-coded. To indicate severity for quantitative symptoms (e.g., temperature, measurements), include the grade in parentheses after the number, e.g., 100.7 (Mild). This listing includes baseline assessments in addition to post-challenge assessments. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Participant ID, Post Challenge Day, Symptom.]

Treatment Group	Participant ID	Post-Challenge Day	Assessment[a]	Symptom	Severity	Attributed to Alternate Etiology?[b]	Alternate Etiology
			MA				
			Clinic				

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

Listing 14: 16.2.7.2: Stool

[Implementation Note: In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Participant ID, Actual Study Day.]

Treatment Group	Participant ID	Post-Challenge Day	Collection Time	Inpatient or Outpatient?	Consistency	Weight (g)	Comments

N/A = Collection of weight of stool sample during the outpatient period was not required. If collected, it may be recorded in the Comments. Laboratory measurements of stool weights are documented in Section 16.2.6 on the Individual Snow Mountain Virus Detection in Stool Data Listing.

Listing 15: 16.2.7.3: Emesis

[Implementation Note: In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Participant ID, Actual Study Day.]

Treatment Group	Participant ID	Post-Challenge Day	Collection Time	Inpatient or Outpatient?	Volume (mL)	Comments

Listing 16: 16.2.7.4: Unsolicited Adverse Events

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. This listing includes all unsolicited adverse events. If there are no comments for an event, populate 'Comments' row with 'None'. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, No. of Days Post-Challenge.]

Adverse Event	No. of Days Post-Challenge (Duration)	Severity	SAE?	NOCMC?	Relationship to Study Treatment	If Not Related, Alternative Etiology	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Participant ID: , AE Number:										
Comments:										
Treatment Group: , Participant ID: , AE Number:										
Comments:										
Note: For additional details about SAEs, see Table: xx.										

16.2.8 Individual Laboratory Measurements

Listing 17: 16.2.8.1: Clinical Laboratory Results – Chemistry

[Implementation Note: These listings include all chemistry results, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., 16.2 (Mild). The "extra" fields that are completed for abnormal results are not included in this listing; they are included in the listing of abnormal laboratory results that is included in the table shells document. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, Laboratory Parameter, and Planned Time Point.]

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

Listing 18: 16.2.8.2: Clinical Laboratory Results – Hematology

[Implementation Note: These listings include all chemistry results, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., 16.2 (Mild). The "extra" fields that are completed for abnormal results are not included in this listing; they are included in the listing of abnormal laboratory results that is included in the table shells document. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, Laboratory Parameter, and Planned Time Point.]

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

Listing 19: 16.2.8.3: Clinical Laboratory Results – Urinalysis

[Implementation Note: These listings include all chemistry results, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., 16.2 (Mild). The "extra" fields that are completed for abnormal results are not included in this listing; they are included in the listing of abnormal laboratory results that is included in the table shells document. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, Laboratory Parameter, and Planned Time Point.]

Treatment Group	Participant 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 20: 16.2.9.1: Vital Signs

[Implementation Note: This listing includes all vital sign assessments, scheduled and unscheduled. This listing is not color-coded, but the severity should be included in parentheses after the result for abnormal assessments, e.g., 100.7 (Mild). In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, Actual Study Day, Temp. Time.]

Treatment Group	Participant ID	Planned Time Point	Actual Study Day	Temp. Time	Temp. (°F) (Severity Grade)	Systolic Blood Pressure Time	Systolic Blood Pressure (mmHg) (Severity Grade)	Diastolic Blood Pressure Time	Diastolic Blood Pressure (mmHg) (Severity Grade)	Pulse Time	Pulse (beats/min) (Severity Grade)

Listing 21: 16.2.9.2: Physical Exam Findings

[Implementation Note: This listing includes all physical exam findings, scheduled and unscheduled. If a participant does not have any findings upon examination, they will not be included in this listing. If reported as an AE, display "Yes" with the AE Number in parentheses, e.g., "Yes (7)". In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: Treatment Group, Participant ID, Actual Study Day.]

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

16.2.10 Concomitant Medications

Listing 22: 16.2.10: Concomitant Medications

[Implementation Note: "Medication Start Day" and "Medication End Day" are relative to enrollment (which is Day 1, day before enrollment is Day -1). For medication start dates that are > 30 days prior to enrollment, rather than use exact study days, categorize as follows:>5 years prior to enrollment, 1-5 years prior to enrollment, 1-12 months prior to enrollment. *If ongoing, display "Ongoing" in the "Medication End Day" column. If taken for an AE or MH, display "Yes" with the AE or MH Number in parentheses, e.g., "Yes (7)". In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, and CM Number.]*

Treatment Group	Participant 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 23: 16.2.11.1: Pregnancy Reports – Maternal Information

[Implementation Note: Only include the "Pregnancy Number" column if a participant has more than 1 pregnancy. Date of Conception will be calculated based on estimated delivery date. BMI will be calculated based on pre-pregnancy height and weight. Mother's weight gain will be calculated based on pre-pregnancy weight and end of pregnancy weight. If a major congenital anomaly with previous pregnancy, display "Yes" and the text from the "specify" field, separated by a colon. If any substance use is reported, include a listing of substance use. If autopsy revealed an alternate etiology, display "Yes" and the text from the "specify" field, separated by a colon. If abnormality in product of conception, display "Yes" and the text from the "specify" field, separated by a colon. In the CSR, Participant ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Participant ID, Pregnancy Number.]

Treatment Group	Participant 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 24: 16.2.11.2: Pregnancy Reports – Gravida and Para

			Live Births												
Participant ID	**Pregnancy Number**	**Gravida**	**Extremely PB[a]**	**Very Early PB[a]**	**Early PB[a]**	**Late PB[a]**	**Early TB[b]**	**Full TB[b]**	**Late TB[b]**	**Post TB[b]**	**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 25: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

Participant 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 26: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

Participant 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 27: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Participant 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

APPENDIX 4. NCA TEMPLATE

See separate document, if applicable.