CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 16-0092
Study Title:
A Phase 2 Multi-Center, Prospective, Randomized, Double-Blind Study to Assess the Clinical and Antiviral Efficacy and Safety of Nitazoxanide for the Treatment of Norovirus in Hematopoietic Stem Cell and Solid Organ Transplant Recipients

NCT03395405

Draft Version 2.0

DATE: August 01, 2022

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 16-0092**
Development Phase:	Phase 2
Products:	56 doses of 500mg Nitazoxanide
Form/Route:	Oral
Indication Studied:	Norovirus
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	15 October 2018
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Version Number:	2.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
CI	Confidence Interval
CRF	Case Report Form
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
ER	Emergency Room
F	Fahrenheit
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
GVHD	Graft vs Host Disease
IBSQOL	Irritable Bowel Syndrome Quality of Life Measure
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention to Treat
L	Liter
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities

List of Abbreviations *(continued)*

mEq	Milliequivalent
mg	Milligram
mITT	Modified Intention to Treat
mL	Milliliter
MAR	Missing at Random
MCAR	Missing Completely at Random
MNAR	Missing Not at Random
N	Number (typically refers to subjects)
NIH	National Institutes of Health
PI	Principal Investigator
PP	Per Protocol
PRO	Patient-Reported Outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
RBC	Red Blood Cell
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedures
TPN	Total Parenteral Nutrition
U	Units
ULN	Upper Limit of Normal
UNOS	United Network for Organ Sharing
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 2 Multi-Center, Prospective, Randomized, Double-Blind Study to Assess the Clinical and Antiviral Efficacy and Safety of Nitazoxanide for the Treatment of Norovirus in Hematopoietic Stem Cell and Solid Organ Transplant Recipients" (DMID Protocol 16-0092) describes and expands upon the statistical information presented in the protocol.

This document describes the analyses planned and provides reasons and justifications for these analyses. Planned analyses for pharmacokinetics (PK) and microbiome endpoints will not be included and will instead be provided in addendums to this SAP. 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 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

Gastroenteritis is defined as a self-limiting diarrheal illness that is often accompanied by nausea, vomiting, fever, or abdominal pain. In the United States, Norovirus is the single most common cause of acute gastroenteritis that leads to medical evaluation in adults, and the second most common cause of severe diarrhea in infants and young children [1, 2]. In the US, Norovirus is estimated to be responsible for 19 – 21 million episodes of gastroenteritis and 56,000 – 71,000 hospitalizations annually. [3] Increasingly, Norovirus is recognized as a common cause of chronic gastroenteritis in immunocompromised patients. Prolonged diarrhea can lead to dehydration, allograft dysfunction, renal insufficiency and rarely death in these patients [1, 4-9].

Noroviruses are small, non-enveloped, single-stranded RNA viruses that are members of the Caliciviridae. (1, 10] Of the five genogroups (GI – GV), GI, GII, and GIV are known to be human pathogens, although most are caused by GI and GII, which can be further classified into 30 unique genotypes. GII.4 has been recognized as the most common cause of outbreaks of Norovirus infections globally. [11, 12]

Norovirus is highly contagious as transmission is highly efficient with a median infectious dose of 18 viruses. There are generally high titers of virus within stool (10^5 to 10^{10} genome copies per gram of feces); [13, 14] therefore contact with infected feces and vomit, fecally-contaminated food, water and surfaces are common sources of infection. Norovirus is also highly stable with retained infectivity under environmental conditions that would generally inactivate other viruses, included chlorine at concentrations used in drinking water. [15, 16].

Norovirus infections typically present as an acute infection in immunocompetent hosts, with an incubation period of 10 to 51 hours. Symptoms include nausea, vomiting, water non-bloody diarrhea, abdominal cramps and occasionally low-grade fever, muscle aches, chills and headache, [16] usually lasting from 20 to 60 hours. [17] While the acute phase of illness is typically short-lived, asymptomatic patients may continue to shed the virus for up to two weeks. [10, 16, 18] Unfortunately, approximately 570 – 800 deaths each year results from Norovirus infections in the US, with one third of fatal cases occurring in immunocompromised hosts. [19]

Immunocompromised patients such as those with congenital immunodeficiencies, human immunodeficiency virus (HIV)-infected patients, solid organ transplant recipients, hematopoietic stem cell transplant patients and oncology patients undergoing chemotherapy can develop chronic Norovirus infections. [1, 20-25] Copious watery diarrhea with stool volume amounting to several liters per day comparable to volumes observed with cholera may last for 3 – 4 months or longer. [3, 21] As a result, dehydration and elevated calcineurin inhibitor levels are common in patients at the time of initial diagnosis.

In vitro, nitazoxanide has been shown to be active against Norovirus. Results from double-blind placebo-controlled studies demonstrate that nitazoxanide decreases the duration of illness in subjects with viral gastroenteritis. Small observational studies suggest that nitazoxanide results in prompt improvement in clinical signs of Norovirus-induced gastroenteritis. Further, nitazoxanide enhanced local production of interferon which may contribute to more rapid clearance of virus. Studies of nitazoxanide for the treatment of Norovirus has presented limited data on quantitative virology and its impact on viral load are less well defined. Further, there are limited data on the impact of nitazoxanide on host and viral changes that may facilitate control and clearance of Norovirus.

The present study is a phase 2 multi-center, prospective, randomized, double-blind study designed to assess the efficacy of nitazoxanide taken twice daily for 28 days compared to placebo for the treatment of Norovirus gastroenteritis in immunosuppressed transplant subjects. Given the safety of prolonged therapy with nitazoxanide [26-29], lack of interactions with common post-transplant medications, putative antiviral activity and prolonged duration of viral shedding we are assessing 28 days of therapy. The longitudinal monitoring

phase will provide useful information on the course of host and viral responses in subjects with chronic Norovirus infection with and without treatment.

2.1. Purpose of the Analyses

These analyses will assess the efficacy and safety of nitazoxanide in comparison with placebo for the management of acute and chronic Norovirus in transplant recipients and will be included in the clinical study report.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective:

- To assess the clinical efficacy of nitazoxanide for the management of acute and chronic Norovirus in transplant recipients.

3.1.2. Secondary Objectives:

- To assess the virologic efficacy of nitazoxanide.
- To assess the safety of nitazoxanide for the management of acute and chronic Norovirus in transplant recipients.

3.1.3. Exploratory Objectives:

- To assess initial clinical improvement in Norovirus Disease through 28 and 180 days.
- To assess markers of virologic improvement in Norovirus Disease through 28 and 180 days.
- To assess the contribution of immunologic response to Norovirus to the clinical course of disease in treated and untreated subjects.
- To define the pharmacokinetics and dose response relationships of nitazoxanide.
- To define the natural history of Norovirus in nitazoxanide treated and untreated subjects.

3.2. Endpoints

3.2.1. Primary Outcome Measure

- The time from randomization until initial clinical resolution of Norovirus symptoms for at least 48 hours through 180 days.

  Clinical resolution will be assessed from the daily diary by the subject and will be defined as:

  - Cessation of vomiting and,
  - No stools classified by the Bristol Stool Chart as diarrhea (Type 6 or 7)

3.2.2. Secondary Efficacy Outcome Measures

- Time from randomization to first negative viral load through 180 days.
- The change in viral titer between Day 1 and 180.

3.2.3. Secondary Safety Outcome Measures

- Incidence of unsolicited non-serious adverse events through 60 days.
- Incidence of laboratory adverse events (White Blood Cell Count (WBC), Hemoglobin, Platelet Count, Creatinine, Alkaline Phosphatase, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Blood Urea Nitrogen (BUN), and Bilirubin) through 60 days.
- Incidence of protocol-specified serious adverse events through 60 days.

- Incidence of hospitalization through 60 days.

3.2.4. Exploratory Outcome Measures

- Time from randomization to initial clinical improvement in Norovirus disease through 28 and 180 days for at least 48 hours, as defined by:
  - 50% reduction in number of episodes of vomiting and,
  - Improvement in PO intake, as judged by the subjects and,
  - 50% reduction in the number of episodes of diarrhea as classified by the subject by the Bristol Stool Chart as type 6 or 7 bowel movements.
- Time from randomization to initial cessation of vomiting through Day 180 (recurrent vomiting will be considered disease recurrence unless determined to be due to another etiology [i.e. GVHD]).
- Time from randomization to subject report of no loss of appetite that is maintained for 48 hours through Day 180 (measure will be first time that the subject reports that they have no "loss of appetite" on their daily diary).
- Time from first dose to initial cessation of diarrhea through Day 180 classified by the Bristol Stool Chart as type 6 or 7 bowel movements (recurrent diarrhea will be considered disease recurrence unless determined to be due to another etiology [i.e. GVHD]).
- Time from randomization to 50% reduction in the amount of antimotility agents utilized by the subject through Day 180.
- Number of days of diarrhea through Days 28 and 180.
- Number of stools classified by the Bristol Stool Chart as type 6 or 7 bowel movements through Day 28.
- Number of days of IV hydration or total parenteral nutrition (TPN) therapy through Day 28.
- Total number of days of hospitalization through Days 28 and 180.
- Change in patient-reported quality of life as measured by EuroQOL-5 (global) and IBSQOL (diarrhea specific) [adult] or EuroQOL-5 Peds (global) and PedsQL GI Module [children] from baseline to Day 180.
- Change in patient-reported physical function as measured by NIH PROMIS Physical Function (Adult) Pediatric Global Health (Peds) from baseline to Day 180.
- Change in patient-reported emotional distress as measured by the NIH PROMIS Depression, Anxiety, Fatigue (Adult and Peds) from baseline to Day 180.
- Change in patient-reported gastrointestinal symptoms as measured by the NIH PROMIS GI (Adult and Peds) symptoms (6 of 8 subscales) from baseline to Day 180.
- The effect of co-pathogens, as determined by the BioFire stool pathogen screen, on the primary outcome measure.
- Time from randomization until initial clinical resolution of Norovirus symptoms for at least 48 hours through Day 180. Clinical resolution will be assessed from the daily diary by the subject and will be defined as cessation of vomiting and no stools classified by the Bristol Stool Chart as diarrhea (Type 6

or 7) from the total population compared to the subgroup of subjects who do not report chromaturia (discoloration of urine) based on unsolicited self-reporting.

- Incidence of unsolicited non-serious adverse events through 60 days, laboratory adverse events (WBC, Hemoglobin, Platelet Count, Creatinine, Alkaline Phosphatase, ALT, AST, BUN, and Bilirubin) through 60 days, protocol-specified serious adverse events through 60 days, and hospitalization through 60 days from the total population compared to the subgroup of subjects who do not report chromaturia (discoloration of urine) based on unsolicited self-reporting
- Time to $\geq$ 1 log reduction in stool Norovirus genome copies.
- Change in quantitative Norovirus load in the stool between Day 1 and Day 7, 14, 21, 28, 60, 120, and 180.
- Change in Norovirus sequence from Day 1 to Days 28 and 60.
- The effect of co-pathogens, as determined by the BioFire stool pathogen screen, on the time from randomization to first negative viral load through 180 days.
- Time from randomization to first negative viral load through 180 days and the change in viral titer between Day 1 and 180 from the total population compared to the subgroup of subjects who do not report chromaturia (discoloration of urine) based on unsolicited self-reporting.
- Change in Norovirus-specific serum and stool IgA, IgM and IgG between Day 1 and Days 28 and 60.
- Association between change in total lymphocyte count and T cell subsets at Day 1 and 180 and clinical resolution of Norovirus symptoms.
- Association between change in total lymphocyte count and T cell subsets at Day 1 and 180 and undetectable quantitative norovirus PCR.
- Association between change in Norovirus-specific serum and stool IgA, IgM and IgG from Day 1 to Days 28 and 60 and clinical resolution of Norovirus symptoms.
- Association between change in Norovirus-specific serum and stool IgA, IgM and IgG from Day 1 to Days 28 and 60 and undetectable quantitative Norovirus PCR.
- For subjects consenting to PK draws, concentrations of nitazoxanide metabolites (tizoxanide and tizoxanide glucuronide) 1 to 4 hours after the first dose on Day 7 and 10 minutes before the second dose on Day 21.
- Time to allograft rejection as per each center team.
- Time to allograft loss as reported to United Network for Organ Sharing (UNOS).
- Time to death.
- Time to withdrawal from the study because of intolerance or drug related adverse events.
- Correlation of secretor status as defined by phenotype and genotype, separately, and clinical resolution of Norovirus as defined by the primary endpoint.

3.3. Study Definitions and Derived Variables

Diarrhea:

Diarrhea will be defined as Type 6 or 7 on the Bristol Stool chart.

Baseline Value:

The baseline value will be defined as the last value obtained prior to the first dose of study product unless otherwise noted.

Additional Nitazoxanide:

Any nitazoxanide reported as a concomitant medication will be considered additional nitazoxanide.

Initial Clinical Resolution of Norovirus Symptoms:

Clinical resolution of Norovirus symptoms will be assessed from the daily diary by the subject and will be defined as:

- Cessation of vomiting and,
- No stools classified by the Bristol Stool Chart as diarrhea (Type 6 or 7).

Subjects will need to have at least two consecutive daily diary entries where they reported no vomiting, no Bristol Stool Type 6, and no Bristol Stool Type 7 to meet the criteria for initial clinical resolution. There are several variables in the daily diary that indicate whether the subject had diarrhea or vomiting for that day.

Daily Diary Diarrhea Questions:

- Phase 1 (Treatment Phase):
  - Number of Bristol Type 6 stools? (Quantitative)
  - Were there too many Bristol Type 6 stools to count? (Qualitative)
  - Number of Bristol Type 7 stools? (Quantitative)
  - Were there too many Bristol Type 7 stools to count? (Qualitative)
- Phase 2 (Longitudinal Phase):
  - Did you have diarrhea today? (By diarrhea, we mean at least ONE bowel movement that could be described as Type 6 or 7.) (Qualitative)

Daily Diary Vomiting Questions:

- Phase 1 (Treatment Phase):
  - Did you have to take another dose because you threw up the first dose within 1 hour? (Qualitative)
  - How many times did you vomit today? (Quantitative)
- Phase 2 (Longitudinal Phase):
  - Did you vomit today? (Qualitative)

For a day to count towards clinical resolution during the treatment phase, the following responses must be recorded in the daily diary entry:

- Both quantitative diarrhea questions must be 0

- Both qualitative diarrhea questions must be missing (i.e. not "yes")
- The quantitative vomiting questions must be 0
- The qualitative vomiting question must be "no"

For a day to count towards clinical resolution during the longitudinal phase, the following responses must be recorded in the daily diary entry:

- The qualitative diarrhea question must be "no"
- The quantitative vomiting question must be 0

If a daily diary entry is missing, refer to the imputation rules in Section 6.5.

Viral Load:

As Norovirus surveillance laboratories have observed that Norovirus type GII is predominant compared to Norovirus type GI and dual infection by both GI and GII viruses is rare, all specimens are tested for Norovirus GII viral load first (Dr. Ming Tan, Dr. Xi Jason Jiang, person communication). Only specimens that are negative for Norovirus GII viral load will be tested for Norovirus GI viral load. Subjects will only be analyzed for the viral load test type (Norovirus GII or Norovirus GI) that they tested positive for at baseline (Visit 01). If a subject initially tested positive for GI and later tested positive for Norovirus GII before they tested negative for Norovirus GI, the subject will be considered positive for Norovirus GI until they test negative for Norovirus GII and Norovirus GI. Subjects that did not test positive for either Norovirus GII or Norovirus GI at baseline will be excluded from the analyses. The first day of undetectable quantitative Norovirus PCR is the first day the subject had either a negative result or a result less than the lower limit of quantitation (LLOQ) for the viral load test type (Norovirus GII or Norovirus GI) that they initially tested positive for at baseline. Viral load will be quantified as the geometric mean of the replicates. Negative results will be imputed as ½ the LLOQ and results greater than the upper limit of quantification (ULOQ) will be imputed as the ULOQ.

Initial Clinical Improvement in Norovirus Disease:

Initial clinical improvement in Norovirus disease through 28 and 180 days for at least 48 hours, is defined by:

a. 50% reduction in number of episodes of vomiting and,
b. Improvement in PO intake, as judged by the subjects and,
c. 50% reduction in the number of episodes of diarrhea as classified by the subject by the Bristol Stool Chart as type 6 or 7 bowel movements.

The baseline values for number of episodes of vomiting and diarrhea will be the numbers provided on the first non-missing daily diary entry for the vomiting and diarrhea questions, respectively. Subjects must answer "yes" to the daily diary question "Did you eat your usual diet today?" to meet the improvement in PO intake criteria.

Detailed Patient-Reported Outcome (PRO) Measures:

Study personnel will administer detailed PRO questionnaires to subjects at Visit 01 (Day 1), Visit 05 (Day 28), Visit 08 (Day 60), Visit 10 (Day 120), and Visit 12 (Day 180).

Quality of Life.

Adult subjects will complete two questionnaires for quality of life: NNITS PRO EuroQOL-5 and NNITS PRO IBSQOL [30]. There were no pediatric subjects enrolled in the study. The IBSQOL contains 34 items, each with a five-point response scale. The score for each subject/visit will be:

$$Score_{IBSQOL} = \frac{The\ sum\ of\ the\ items - lowest\ possible\ score}{possible\ raw\ score\ range} \times 100$$

If items are missing, confirm that at least 17 (50%) have been answered before calculating the score. If less than 17 questions have been answered, the score will be left as missing.

The scoring guide for the EuroQOL-5 questionnaire [31] states that a single index value is not currently possible. Instead, the levels will be dichotomized into 'no problems' (i.e. level 1) and 'problems' (i.e. levels 2 and 3).

Patient-Reported Physical Function:

Adult subjects will complete the NNITS PRO PROMIS [32] Physical Function questionnaire. The raw score will be the sum of the items from the questionnaire. The score for each subject/visit will then use the following table to convert the raw score into a t-score:

Physical Function 8b
Short Form Conversion Table

Raw Score	T-score	SE*
8	20.9	3.5
9	24.4	2.5
10	26.4	2.2
11	27.9	2.0
12	29.1	1.9
13	30.1	1.8
14	31.1	1.7
15	31.9	1.7
16	32.7	1.6
17	33.4	1.6
18	34.1	1.6
19	34.8	1.6
20	35.5	1.6
21	36.2	1.5
22	36.8	1.5
23	37.5	1.5
24	38.1	1.5
25	38.8	1.5
26	39.4	1.5
27	40.1	1.6
28	40.8	1.6
29	41.5	1.6
30	42.2	1.6
31	43.0	1.6
32	43.7	1.6
33	44.6	1.7
34	45.5	1.7
35	46.4	1.8
36	47.5	1.9
37	48.8	2.1
38	50.4	2.5
39	52.5	2.9
40	59.7	5.9

* SE = Standard error

Adult version

If items are missing, confirm that at least 4 (50%) have been answered before calculating the score. If less than 4 questions have been answered, the score will be left as missing. If less than 4 items are missing, the pro-rated raw score will be:

$$Raw\ score = \frac{Raw\ sum\ \times 8}{Number\ of\ items\ that\ were\ actually\ answered}$$

If the result is a fraction, round up to the nearest whole number.

Patient-Reported Emotional Distress:

Adult subjects will complete the NNITS PROMIS Emotional Questionnaire. Patient-reported emotional distress will be reported in three separate categories: depression, anxiety, and fatigue.

The raw score for depression will be the sum of questions #1-4. The depression score for each subject/visit will then use the following table to convert the raw score into a t-score:

Depression 4a
Short Form Conversion Table

Raw Score	T-score	SE*
4	41.0	6.2
5	49.0	3.2
6	51.8	2.7
7	53.9	2.4
8	55.7	2.3
9	57.3	2.3
10	58.9	2.3
11	60.5	2.3
12	62.2	2.3
13	63.9	2.3
14	65.7	2.3
15	67.5	2.3
16	69.4	2.3
17	71.2	2.4
18	73.3	2.4
19	75.7	2.6
20	79.4	3.6

*SE = Standard Error

All questions must be answered to receive a depression score.

The raw score for anxiety will be the sum of questions #5-8. The anxiety score for each subject/visit will then use the following table to convert the raw score into a t-score:

Anxiety 4a
Short Form Conversion Table

Raw Score	T-score	SE*
4	40.3	6.1
5	48.0	3.6
6	51.2	3.1
7	53.7	2.8
8	55.8	2.7
9	57.7	2.6
10	59.5	2.6
11	61.4	2.6
12	63.4	2.6
13	65.3	2.7
14	67.3	2.7
15	69.3	2.7
16	71.2	2.7
17	73.3	2.7
18	75.4	2.7
19	77.9	2.9
20	81.6	3.7

*SE = Standard Error

All questions must be answered to receive an anxiety score.

The raw score for fatigue will be the sum of questions #9-12. The fatigue score for each subject/visit will then use the following table to convert the raw score into a t-score:

Fatigue 4a
Short Form Conversion Table

Raw Score	T-score	SE*
4	33.7	4.9
5	39.7	3.1
6	43.1	2.7
7	46.0	2.6
8	48.6	2.5
9	51.0	2.5
10	53.1	2.4
11	55.1	2.4
12	57.0	2.3
13	58.8	2.3
14	60.7	2.3
15	62.7	2.4
16	64.6	2.4
17	66.7	2.4
18	69.0	2.5
19	71.6	2.7
20	75.8	3.9

*SE = Standard Error

All questions must be answered to receive a fatigue score.

Patient-Reported Gastrointestinal Symptoms:

Adult subjects will complete the NNITS PROMIS GI Questionnaire. For question 17, each belly pain area marked "yes" will indicate 1 point (e.g. if a subject answers "yes" for belly pain area 1, belly pain area 6, and belly pain area 8, their score for question 17 would be 3). The GI Questionnaire contains questions from four domains: diarrhea (questions 1 – 3 and 8 – 10), nausea (questions 4 – 7), fecal incontinence (questions 11 – 14), and belly pain (questions 15 – 20) and therefore cannot be summarized into a single score. Instead each domain will be reported separately. The raw scores for each domain will be the sum of the items from the questionnaire that are in the domain. The score for each subject/visit will then use the following tables to convert the raw scores into t-scores:

Diarrhea:

Raw score	T-score
0	38.3
1	43.3
2	45.9
3	48.2
4	50.1
5	51.9
6	53.3
7	54.5
8	55.6
9	56.7
10	57.8
11	58.8
12	59.8
13	60.7
14	61.6
15	62.5
16	63.5
17	64.4
18	65.5
19	66.6
20	67.9
21	69.2
22	70.8
23	72.3
24	75.2

Nausea:

Raw score	T-score
0	40.3
1	45.0
2	49.3
3	52.9
4	55.9
5	58.7
6	60.9
7	62.8
8	64.6
9	66.4
10	68.1
11	69.8
12	71.6
13	73.5
14	75.6
15	78.0
16	80.4

Fecal Incontinence:

Raw score	T-score
0	42.0
1	49.1
2	54.4
3	58.6
4	62.1
5	64.4
6	66.0
7	67.7
8	69.5
9	71.4
10	73.5
11	75.8
12	78.4
13	80.8
14	80.8
15	80.8
16	80.8

Belly Pain:

Raw score	T-score
0	31.7
1	37.2
2	40.6
3	43.5
4	46.2
5	48.6
6	50.7
7	52.6
8	54.3
9	55.9
10	57.5
11	59.1
12	60.5
13	61.9
14	63.2
15	64.5
16	65.8
17	67.0
18	68.3
19	69.5
20	70.8
21	72.1
22	73.5
23	74.9
24	76.1
25	76.9
26	77.9
27	78.6
28	78.6
29	82.1

If items are missing, confirm that at least 50% have been answered before calculating the score. If less than 50% of the questions have been answered, the score will be left as missing. If less than 50% of the items are missing, the pro-rated raw score will be:

$$Raw\ score = \frac{Raw\ sum\ \times Total\ number\ of\ questions\ in\ domain}{Number\ of\ items\ that\ were\ actually\ answered}$$

If the result is a fraction, round up to the nearest whole number. Note that only three of the four nausea questions from the GI questionnaire were included, therefore in order to meet the 50% criteria at least 2 of the 3 questions must be answered.

Positive and Negative Affect Scale (PANAS):

Adult subjects will complete the NNITS PROMIS PANAS Questionnaire. Patient-reported positive and negative affect scores will be reported in two separate categories: positive affect score and negative affect score.

The score for positive affect will be the sum of questions #1, 3, 5, 9, 10, 12, 14, 16, 17, and 19. The score for negative affect will be the sum of questions #2, 4, 6, 7, 8, 11, 13, 15, 18, and 20.

Reduction in Amount of Antimotility Agents:

The amount of antimotility agents for a given day will be defined as the response to the "# of antidiarrheals today" question in the Phase 1 (Treatment Phase) Daily Symptom Diary. Missing responses will be left as missing. 50% reduction in the amount of antimotility agents will be defined as the first study day in which the subject's response was less than or equal to 50% of their response given on Day 1.

Number of Days of Diarrhea:

The number of days of diarrhea will be based on the Daily Diary Diarrhea Questions (see above). For a day to count towards the number of days of diarrhea, one of the following must occur: a quantitative diarrhea question must be greater than 0 or a qualitative question must be marked "yes". Missing responses will be left as missing.

Number of Type 6 or 7 Stools:

The number of Type 6 or 7 stools through Day 28 will be defined as the sum of the responses to the quantitative Daily Diary Diarrhea Questions during the Treatment Phase (see above). Missing responses will be left as missing.

Number of Days of IV Hydration or Total Parenteral Nutrition (TPN) Therapy:

The number of days of IV hydration or TPN therapy will be defined as the number of days with a concomitant medication with any indication related to IV hydration or TPN therapy. A blinded review of the concomitant medication data will be performed by the Medical Monitor to identify medications that should be included in the analysis. Days prior to Day 1 will not be included in the calculation of the number of days. Medications that are ongoing after Day 28 will be censored at 28 days.

Co-pathogen Status:

Co-pathogen status will be determined by the BioFire stool pathogen screen on Days 1 and 180. Co-pathogen status will be determined on Days 7, 14, 21, 28, 60, 120, and with recurrent diarrhea if unformed stool is present on study day. Analyses will only include whether pathogens were detected or not and will not differentiate by co-pathogen type. The listing will include which co-pathogens were detected at each subject/visit (Listing 18).

Secretor Status:

Saliva is collected at screening to determine H type 1 secretor status (phenotyping), while a buccal swab is collected to perform FUT2 genotyping. Phenotype and genotype results will either be "secretor" or "non-secretor" for each subject.

Norovirus-Specific Immunoglobulins (Ig):

Results below the lower limit of detection (LLOD) will be imputed as ½ the LLOD. Results above the upper limit of detection (ULOD) will be imputed as the ULOD.

Responders:

A subject is classified as a responder if he or she has a four-fold or greater increase in Norovirus-specific Ig titers compared to baseline (Day 1).

Study Day:

Study day will be reported as the number of days from randomization with the day of randomization reported as study day 1.

Days Post-Randomization:

Days post-randomization will be reported as the number of days since randomization; if an event began on the day of randomization, the days post-randomization is reported as 0.

Duration:

Duration will be reported as the difference between the start and end dates, inclusive of the day the event started.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

A total of 160 subjects ≥ 12 years of age will be selected according to the inclusion and exclusion criteria. Upon enrollment in the study, subjects will be randomized into two treatment groups: active nitazoxanide and placebo. The nitazoxanide arm will be given one 500mg tablet of nitazoxanide by mouth twice daily with food for 56 consecutive doses. The placebo arm will be given one placebo tablet by mouth twice daily with food for 56 consecutive doses. Randomization will be stratified by age group (pediatric (12-17 years) vs. adult (≥ 18 years)), chronicity of Norovirus-associated symptoms (acute (<14 days) vs. chronic (≥14 days)) and transplant type (solid organ (SOT) vs. hematopoietic stem cell transplant (HSCT)). Enrolled subjects will participate in 2 phases of the study: Treatment Phase, which will include dosing with the assigned study agent for 28 days and study visits on study Day 1, 7 ± 3 days, 14 ± 3 days, 21 ± 3 days, and 28 + 3 days; Longitudinal Monitoring Phase which will include telephone call on Days 35 ± 3 days, 53 ± 7 days, 113 ± 7 days, and 173 ± 7 days, and study visits on study Day 60 ± 14 days, 120 ± 14 days and 180 ± 14 days. If symptoms recur after completion of the Treatment Phase, subjects can resume any therapy excluding nitazoxanide at the discretion of the principal investigator or his/her designee. Nitazoxanide can be used after Day 28 if the local PI attests that it is medically urgent to use the nitazoxanide because the patient is experiencing severe or life-threatening disease. Although nitazoxanide can be used if it is felt critical to the subject's care, its use should be avoided until Day 180 whenever felt to be safe to do so by the local PI. Additional stool specimens should be collected prior to initiation of therapy for testing in the central lab.

Figure 1 presents the schematic of the study design.

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

Subjects are randomized at a ratio of 1:1 to receive one 500mg tablet of nitazoxanide or one placebo tablet by mouth twice daily with food for 28 days (56 consecutive doses).

4.3. Selection of Study Population

All candidates at all centers who meet all eligibility requirements will be offered the opportunity to participate in the trial. Study subjects are seen in patient or clinic setting and have either community onset or hospital acquired disease.

Inclusion Criteria

Subjects should meet all of the following inclusion criteria:

1. Male or female age ≥ 12 years.
2. Recipient of a solid organ or hematopoietic stem cell transplant.
3. Positive test result for Norovirus within 14 days of enrollment that is obtained as part of routine clinical care using a Norovirus testing available to the site.
4. Active GI symptoms (diarrhea or vomiting) that, in the opinion of the PI, are secondary to Norovirus.[#]
   [#] Patients must have active diarrhea, which is defined as at least 3 days of Bristol 6 or 7 stools in the past 2 weeks prior to enrollment per patient report.
5. Willing and able to provide written informed consent and assent before initiation of any study procedures, consistent with local IRB policy.

6. Subjects must be of non-childbearing potential or if of childbearing potential, must be using an effective method of birth control or must be abstinent.
    - Non-childbearing potential is defined as surgically sterile or postmenopausal for > one year.
    - Effective methods of birth control include the use of hormonal or barrier birth control such as implants, injectable contraceptives, combined oral contraceptives, intrauterine devices [IUDs] or condoms with spermicidal agents during study period. Female subjects must be using an effective method of birth control or practice abstinence and must agree to continue such precautions during the study and for 30 days after the Day 28 study visit.
    - A woman is eligible if she is monogamous with a vasectomized male. This subject is considered low risk and not required to use contraception.
7. Agrees to complete all screening requirements, study visits and procedures.

Exclusion Criteria:

Subjects meeting any of the following exclusion criteria at baseline will be excluded from study participation:

1. Other identified infectious causes of diarrhea at screening*.
   *Alternative diagnosis requiring treatment would be considered a co-infection; if the testing is positive for a pathogen that the PI does not feel is causing the symptoms, they may be included but the PI or his/her designee must document that the positive test is not clinically significant, does not require treatment and is not causing the symptoms making the patient eligible for enrollment
2. Any condition that would, in opinion of the Site Investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.
3. Subjects receiving oral or intravenous immunoglobulin therapy concurrently or in the 14 days prior to enrollment.
4. Nitazoxanide use for any illness in the previous 30 days prior to randomization.
5. Have received experimental products within 30 days prior to the study entry or plan to receive experimental products at any time during the study
6. Known sensitivity to nitazoxanide or any of the excipients comprising the nitazoxanide tablets.
7. Subjects unable to swallow oral medications.
8. Subjects with ostomy.
9. Women who are pregnant or lactating or have a positive urine pregnancy test at screening/enrollment/Day 1.

Co-enrollment in other studies is allowed if none of the above exclusion criteria are met.

4.4. Treatments

4.4.1. Treatments Administered

Subjects will be randomized to receive either one 500 mg tablet of nitazoxanide twice daily with food for 56 consecutive doses, or placebo. Nitazoxanide is a synthetic antiprotozoal agent for oral administration. The placebo will look identical to nitazoxanide and will have the same inactive ingredients.

4.4.2. Identity of Investigational Product(s)

Nitazoxanide Tablets:

Nitazoxanide will be supplied as a 500 mg round, yellow, film-coated tablet with "CTM" imprint, manufactured by Romark, L.C. Per the package insert, inactive ingredients include: maize starch, pregelatinized corn starch, hydroxypropyl methylcellulose, sucrose, sodium starch glycollate, talc, magnesium stearate, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, FD&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake.

Placebo Tablets:

Placebo will be supplied as a matching tablet of the active drug which will also be a round, yellow, film-coated tablet with "CTM" imprint. Ingredients include: lactose monohydrate, magnesium stearate, talc, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, FD&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake. In order to maintain the blind, the placebo will be formulated for the same appearance as the active study drug.

All study product will be packaged in two 60cc identical containers each containing 30 tablets. Each container will also be labeled in compliance with applicable regulatory requirements, including the FDA-required cautionary statement "Caution: - New drug -Limited by Federal Law to Investigational Use."

Upon request from DMID, the study products will be shipped from the manufacturer to the DMID Clinical Materials Services (CMS). Study products will be shipped from the DMID CMS to investigational site upon request and approval from DMID.

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

Enrollment of subjects will be done online using the enrollment module of Advantage eClinical. Eligible subjects will be randomized and assigned in a 1:1 ratio to active nitazoxanide or placebo. The study will use a stratified, permuted block randomization scheme. Permuted block randomization is used to avoid the potential for serious imbalance in the number of subjects assigned to each group, an imbalance that can occur in the simple randomization procedures.

Stratification will be by:

- Duration of symptoms: onset of Norovirus-associated symptoms (diarrhea, nausea and/or abnormal appetite) < 14 days vs. ≥ 14 days
- Transplant Type: solid organ vs hematopoietic stem cell transplant
- Age Range: pediatric (12-17 years) vs. adult ≥ 18 years

The randomization list will be computer-generated by statisticians at the Statistical and Data Coordinating Center (SDCC) using a stratified, permuted block randomization scheme and is included in the enrollment module for the trial. Advantage eClinical will assign each subject to a treatment group after the demographic, duration of symptoms, transplant type, and eligibility data have been entered into the system.

Each site will have a supply of two 60cc identical blinded bottles pre-labeled with randomization numbers, each containing 30 tablets, sufficient to treat a subject with 56 doses. The two identical containers will be packaged in the same plastic bag. Once a subject is assigned a randomization number, the corresponding bottles will be distributed to the subject.

4.4.4. Selection of Doses in the Study

Subjects will receive either one 500 mg tablet of nitazoxanide twice daily with food for 56 consecutive doses, or placebo. In vitro, nitazoxanide has been shown to be active against Norovirus. Results from double-blind placebo-controlled studies demonstrate that nitazoxanide decreases the duration of illness in subjects with viral gastroenteritis. Small observational studies suggest that nitazoxanide results in prompt improvement in clinical signs of Norovirus-induced gastroenteritis. Further, nitazoxanide enhanced local production of interferon which may contribute to more rapid clearance of virus.

Given the safety of prolonged therapy with nitazoxanide [26-29], lack of interactions with common post-transplant medications, putative antiviral activity and prolonged duration of viral shedding we are assessing 28 days of therapy.

4.4.5. Selection and Timing of Dose for Each Subject

Nitazoxanide (administered orally as one 500 mg tablet) or placebo (administered orally as a matching tablet) twice daily with food for 56 doses. If the patient is NPO, product can be taken with water.

Subjects in the hospital will be provided the study drug consistent with the site SOP while ambulatory subjects will be provided two bottles, each containing 30 tablets.

If the subject has an episode of emesis or spits out the study medication within one hour of administration, the event will be documented in the Subject Diary and then the full dose will be re-administered. Replacement medication can only be taken one time per scheduled dose.

Within a 24-hour period, the first and second dose should not be taken less than 8 hours apart.

If a subject misses a dose, they will be instructed to skip that dose and resume taking their next dose as scheduled and to record the missed dose on their Subject Diary.

4.4.6. Blinding

Study product will be distributed by a site research pharmacist or other authorized healthcare provider at the site via a pre-labeled kit containing two labeled bottles. All study assessments will be performed by blinded study personnel. All other staff, as well as all subjects, will be blinded to treatment assignment. Samples provided to the lab for virologic, immunogenic, and pharmacokinetic analyses will be blinded to Subject ID and visit number in addition to treatment assignment.

The Principal Investigator should be available to review and evaluate any notable reactions. In the case of a medical emergency, the PI or Secondary Medical Assessor (SMA) may deem it medically necessary to unblind the subject's treatment assignment. If the PI or SMA believes that unblinding would benefit the medical care of the subject and time permits, DMID will be consulted prior to unblinding, and concurrence will be obtained.

The PI, or SMA will contact the study PI, and DMID Medical Monitor (or designees) to confirm that the unblinded treatment assignment is required for the safety of the subject and treatment of their symptoms. The Northwestern University Principal Investigator and DMID Medical Monitor will obtain approval from the Director of the Office of Clinical Research Affairs. After DMID has approved the unblinding, the Medical Monitor will relate the request to Emmes.

Emmes will provide the treatment assignment to an independent medical doctor or appropriate designee identified by the study PI, who is NOT the principal investigator or blinded staff at the clinical site. The treatment assignment will be distributed a secure, restricted access posting on the Emmes website (or

verbally, if it is an emergency). The person receiving the information should not be involved in any subject assessments to maintain the blind, and it cannot be shared with other staff or DMID.

4.4.7. Prior and Concomitant Therapy

Subjects may receive any therapy that is deemed appropriate to treat the signs and symptoms of Norovirus after randomization at the discretion of their treating provider except for nitazoxanide and oral immunoglobulin. This can include:

- Intravenous immunoglobulin
- Changes in immunosuppression
- Anti-motility agents

Any treatment utilized should be included on the concomitant medications at the time of enrollment. Any concomitant medication pre- or post-randomizations that is being used to treat the signs or symptoms of Norovirus should be marked as such on the Case Report Form for the entire duration of the study. Likewise, any change to immunosuppressive therapy would have a note in the Case Report Form noting if the change was made because of elevated drug levels, for treatment of Norovirus or other purposes. Concomitant medications will be collected through visit 12 (Day 180 after initial dose of study treatment) or early termination, whichever occurs first. If the Investigator learns that the subject has taken a prohibited medication (see inclusion/exclusion criteria) prior to the last dose, the Investigator will contact the DMID Medical Officer and CPM for instructions regarding the subject's continuation in the study.

Medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary.

If symptoms recur after discontinuing therapy, subjects can resume any therapy at the discretion of the principal investigator or his/her designee with the exception of nitazoxanide. Nitazoxanide can be used after Day 28 if the local PI attests that it is medically urgent to use the nitazoxanide because the patient is experiencing severe or life-threatening disease. Although nitazoxanide can be used if it is felt critical to the subjects care, its use should be avoided until Day 180 whenever felt to be safe to do so by the local PI. Any use of nitazoxanide beyond Day 28 will be documented on the concomitant medication form and prescribed from commercial stock and not provided by the study.

4.4.8. Treatment Compliance

Each subject will receive 2 bottles of nitazoxanide or placebo each containing 30 tablets, to be taken twice a day for 56 consecutive doses. If study subject has an episode of emesis or spits out the study medication within one hour of administration, the event will be documented in the subject's record and then the full dose will be re-administered one time only per scheduled dose. Subjects will be requested to bring study drug with them to all visits during the Treatment Phase. Remaining pill count will be done by the site staff during each visit to assess compliance. If subjects forget to bring in their study drug or they lose their container, subject interview and study diary will be used to confirm medication adherence.

4.5. Efficacy, Immunogenicity, Safety, and Other Variables

Stool and blood samples will be collected at different visits as per the schedule of events (Table 1).

4.5.1. Efficacy Variables

The primary efficacy variables to be assessed are the cessation of vomiting and no stools classified by the Bristol Stool Chart as diarrhea (Type 6 or 7) and are based on outcomes reported in the Subject Daily Diary. The subject diaries were prepared by Northwestern University. They will be reviewed and collected at every visit, including unscheduled or early termination visits. The Subject Daily Symptom Dairies will be completed by the subject daily, in real-time, from Day 1 through Day 180. All diaries should be completed at the same time every day, when possible. Subjects will complete the NNITS Daily Symptom Diary [Day 1 – 28] from the time of study treatment dispensation until visit 05. At visit 05 (Study Day 28), subjects will complete the NNITS Daily Symptom Diary – Post Treatment [Day 29 – 180].

The exploratory efficacy variables for the following outcome measures are also based on subject daily diaries:

- Time from randomization to initial clinical improvement in Norovirus disease through 28 and 180 days for at least 48 hours.
- Time from randomization to initial cessation of vomiting through Day 180 (recurrent vomiting will be considered disease recurrence unless determined to be due to another etiology [i.e. GVHD]).
- Time from randomization to subject report of no loss of appetite that is maintained for 48 hours through Day 180 (measure will be first time that the subject reports that they have no "loss of appetite" on their daily diary).
- Time from randomization to initial cessation of diarrhea through Day 180 classified by the Bristol Stool Chart as type 6 or 7 bowel movements (recurrent diarrhea will be considered disease recurrence unless determined to be due to another etiology [i.e. GVHD]).
- Time from randomization to 50% reduction in the amount of antimotility agents utilized by the subject through Day 180.
- Number of days of diarrhea through Days 28 and 180.
- Number of stools classified by the Bristol Stool Chart as type 6 or 7 bowel movements through Day 28.
- Number of days of IV hydration or total parenteral nutrition (TPN) therapy through Day 28.

The secondary efficacy variable to be assessed is viral load and is based on stool for Norovirus assays. Norovirus viral load assays will be performed in the Jiang Laboratory (CCHMC, Cincinnati, OH) and will be measured using Quantitative RT-PCR (qRT-PCR) at Study Days 1, 7, 14, 21, 28, 60, 120, 180, and with recurrent diarrhea.

The exploratory efficacy variables for the following outcome measures are based on patient reported outcome (PRO) questionnaires:

- Change in patient-reported quality of life as measured by EuroQOL-5 (global) and IBSQOL (diarrhea specific) [adult] or EuroQOL-5 Peds (global) and PedsQL GI Module [children] from baseline to Day 180.
- Change in patient-reported physical function as measured by NIH PROMIS Physical Function (Adult) Pediatric Global Health (Peds) from baseline to Day 180.
- Change in patient-reported emotional distress as measured by the NIH PROMIS Depression, Anxiety, Fatigue (Adult and Peds) from baseline to Day 180.

- Change in patient-reported gastrointestinal symptoms as measured by the NIH PROMIS GI (Adult and Peds) symptoms (6 of 8 subscales) from baseline to Day 180.

The PRO questionnaires were prepared by Northwestern University. Study personnel administer detailed PRO questionnaires to subjects at Visit 01 (Day 1), Visit 05 (Day 28), Visit 08 (Day 60), Visit 10 (Day 120), and Visit 12 (Day 180). Adult subjects will complete the following six questionnaires:

- NNITS Patient Reported Outcome Measures – IBSQOL Questionnaire (labeled Norovirus QOL)
- NNITS Patient Reported Outcome Measures – EuroQOL Questionnaire
- NNITS Patient Reported Outcome Measures – PROMIS Emotional Questionnaire
- NNITS Patient Reported Outcome Measures – PROMIS GI Questionnaire (labeled Gastrointestinal Symptom Scale)
- NNITS Patient Reported Outcome Measures – PANAS Questionnaire
- NNITS Patient Reported Outcome Measures – PROMIS Physical Function Questionnaire

Pediatric subjects will complete the following six questionnaires:

- NNITS Patient Reported Outcome Measures – PedsQL GI Questionnaire (labeled PedsQL 3.0 Gastrointestinal Symptoms Scale)
- NNITS Patient Reported Outcome Measures – EuroQOL Questionnaire
- NNITS Patient Reported Outcome Measures – PROMIS Emotional Pediatric Questionnaire
- NNITS Patient Reported Outcome Measures – PROMIS GI Questionnaire (labeled Gastrointestinal Symptom Scale; labeled “Adult”)
- NNITS Patient Reported Outcome Measures – PANAS-C Questionnaire
- NNITS Patient Reported Outcome Measures – PROMIS Global Health Questionnaire

Additional exploratory efficacy variables include chromaturia and co-pathogens. Chromaturia (discoloration of urine) will be based on unsolicited self-reporting. Co-pathogen status in stool will be determined utilizing the BioFire FilmArray Gastrointestinal Panel to screen for a range of pathogens (*Campylobacter* (*C. jejuni/C. coli/C. upsaliensis*),*Clostridium difficile* (*C. difficile*) toxin A/B, *Plesiomonas shigelloides, Salmonella, Vibrio* (*V. parahaemolyticus/V. vulnificus/ V. cholerae*), including specific identification of *Vibrio cholerae, Yersinia enterocolitica,* Enteroaggregative *Escherichia coli* (EAEC), Enteropathogenic *Escherichia coli* (EPEC), Enterotoxigenic *Escherichia coli* (ETEC) *lt/st,* Shiga-like toxin-producing *Escherichia coli* (STEC) *stx1/stx2* (including specific identification of the *E. coli* O157serogroup within STEC), *Shigella*/ Enteroinvasive *Escherichia coli* (EIEC), *Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica, Giardia lamblia* (also known as *G. intestinalis* and *G. duodenalis*), Adenovirus F 40/41, Astrovirus, Norovirus GI/GII, Rotavirus A, Sapovirus (Genogroups I, II, IV, and V)). Pathogen screening will occur on Days 1 and 180 for all subjects along with Days 7, 14, 21, 28, 60, 120, and with recurrent diarrhea if unformed stool on study day.

4.5.2. Immunogenicity Variables

Exploratory immunogenicity variables will be measured in the Jiang Laboratory (CCHMC, Cincinnati, OH) by the following assays:

- Norovirus-specific stool IgA, IgM, and IgG results
- Quantitative Total IgG Level results
- Norovirus-specific serum IgA, IgM, and IgG results

All immunogenicity variables are measured using an EIA spectra reader on Days 1, 28, and 60 and will include positive and negative controls. The Norovirus-specific ELISAs will be performed for subjects after the sample genotyping has been completed and the antigens in the ELISAs will match their genotype.

Total lymphocyte count and t cell subsets will be measured at Day 1. T cell subset will not be drawn if the CBC shows an ALC<100.

4.5.3. Safety Variables

The safety of nitazoxanide will be assessed by the frequency of protocol specified unsolicited clinical adverse events, laboratory adverse events and serious adverse events.

Unsolicited Adverse Events (AEs):

Unsolicited clinical Adverse Events are those non serious AEs that are not being collected as clinical outcome measures. For this study, unsolicited clinical AEs to be captured on the appropriate case report form, will be only those clinical AEs that meet either of the following criteria through 60 days:

- Result in modification in the administration of the study drug (nitazoxanide or placebo).
- Result in discontinuation of the study drug (nitazoxanide or placebo).

Any medical condition that is present at the time that the subject is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE as defined above.

Unsolicited clinical AEs will be assigned the severity level of Grade 3.

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

Safety Laboratory Parameters:

The following solicited safety laboratory parameters will be assessed on Day 7, 28 and 60: WBC, Hemoglobin, Platelet count, Creatinine, Alkaline Phosphatase, ALT, AST, BUN and Bilirubin. Additional laboratory parameters performed as part of the CBC and complete metabolic panel results need to be recorded in the source document with the evaluation of the site physician. Those additional laboratory values will need to be reported as AEs only if clinically significant and not attributable to Norovirus infection or underlying SOT/HSCT medical conditions.

Abnormal values observed in the clinical laboratory assessment that are conducted by the clinical team outside the study visits, will be reported as AEs only if the site physician assesses that the laboratory value is clinically significant and not attributable to Norovirus infection or underlying SOT/HSCT medical conditions. The criteria for an abnormal laboratory test finding being classified as an AE are any of the following and will be documented on the AE form:

- Test result is associated with a sign or symptom, and/or
- Test result requires additional diagnostic testing, and/or
- Test result requires a medical or surgical intervention, and/or
- Test result leads to a change in study dosing outside of the protocol defined dosing or discontinuation from the study treatment, and/or
- Test result requires significant additional treatment, i.e. addition of new medication, significant increase in dose of current medication

Baseline clinical labs performed on Day 1 (screening/enrollment visit) might fall outside of the normal range. Laboratory values in all subsequent visits for subjects in which baseline clinical labs results fall outside the normal range will be considered adverse events only if there is a worsening in the grading of the event (e.g., value that on screening falls within grade 1, and subsequently on grade 2 will be considered AE; value that on both screening and on subsequent testing fall within grade 2 will not be considered AE).

For those clinical labs performed on Day 1 that fall within grade 3, for all subsequent testing that also falls within grade 3, the clinician will need to assess and document this assessment on the source documents whether there is a clinically significant worsening of the value. Only those laboratory values judged to have a clinically significant worsening and not attributable to Norovirus infection or underlying SOT/HSCT medical conditions will be reported as AEs.

The protocol defined grading system is used to determine the cut off point for reporting. As such, laboratory results that are abnormal according to the local laboratory reference range but not considered a Grade 1 abnormality, will not be considered laboratory AEs. Those events will be followed-up clinically at the discretion of the study site physician.

Laboratory AEs will be assessed by the clinician using a protocol defined grading system (Table 5).

Serious Adverse Events (SAEs):

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the site principal investigator or sponsor, it results in any of the following outcomes through Day 60:

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

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

Note that hospitalizations are being collected as an outcome measure for the secondary objective and therefore will not be reported as SAEs.

All protocol specified SAEs will be assigned the severity level of Grade 3.

4.5.4. Other Variables

Additional variables to be assessed include graft rejection or graft loss. These will not be entered as unsolicited adverse events but instead entered on the Graft Rejection or Loss eCRF.

Time to death variable will be assessed using the date of death located on the Death eCRF.

Time to withdrawal from the study because of intolerance or drug related adverse events will be assessed using the date treatment discontinued on the Study Status eCRF for all subjects that terminated early. Reasons for early termination will undergo a review, blinded to outcome value, to determine if the withdrawal was due to intolerance or a drug related adverse event.

Saliva is collected on Day 1 to determine H type 1 secretor status (phenotyping) and a buccal swab is also collected to perform FUT2 genotyping. Secretor status will be measured in the Jiang Laboratory (CCHMC, Cincinnati, OH). Both phenotypic and genotypic evaluation will be performed to compare results of the two methods. Detection of secretor antigens (Le^b, Le^y, H types) and non-secretor antigens (Le^a and Le^x) will be performed using monoclonal antibodies by ELISA. In the case of discordant results, the results from the phenotypic method will be used to classify secretor status.

5. SAMPLE SIZE CONSIDERATIONS

Sample size calculations assume a 50% reduction in the median duration of diarrhea for the nitazoxanide-treated group compared to those receiving placebo. The median diarrhea duration for the placebo group is assumed to be 135 days, while the median diarrhea duration for the treatment group is assumed to be 67.5 days. Given these assumptions, a sample size of 64 subjects in each arm (128 total) is required to achieve 90% power using the Log-Rank test. Accounting for a 20% attrition rate, final sample size will be 80 in each arm (160 total).

Though discouraged, the protocol allows for subjects in either study group to receive additional nitazoxanide after 28 days. Under the assumptions of treatment efficacy, additional treatment received by placebo subjects would reduce the median duration of symptoms for the placebo group to be closer to that of the nitazoxanide-treated group. It is assumed that subjects who would have the worst study outcomes (longest time to clinical resolution of diarrhea) will be the most likely to receive additional treatment. Subjects receiving additional treatment will be imputed as having the worst outcome (time to resolution censored at 180 days). Accounting for this imputation method, the power attained for the primary comparison was computed via simulation (R version 3.0.3). Estimated power is displayed in Table 2, varying the proportion of subjects in each study group who receive additional treatment.

For example, if 15% of placebo subjects receive nitazoxanide, and 5-10% of subjects in the nitazoxanide-treated group receive additional treatment, the power is estimated to be 91.2%. Note that implausible scenarios (where substantially more nitazoxanide subjects receive additional treatment than do placebo subjects) have been omitted from the table.

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, minimum, and maximum. 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 site, treatment, and subject, and when appropriate, by visit number within subject. All summary tables will be structured with a column (or row) for each treatment group in the order from left to right (or top to bottom): Nitazoxanide 500 mg, Placebo. Where necessary, summary tables will be stratified with Nitazoxanide 500 mg presented in one table and Placebo presented in the table immediately following. Tables will be annotated with the total population size relevant to that table/treatment, including any missing observations.

6.2. Timing of Analyses

The study was stopped early due to low enrollment and other unforeseen challenges, and thus the primary CSR will be generated once the last subject last visit has occurred, data monitoring and cleaning is complete, and the database is locked. PK and microbiome endpoints will not be included and will instead be provided in addendums to the CSR.

6.3. Analysis Populations

A tabular listing of all subjects excluded from the analysis populations will be provided in the CSR (Listing 5).

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

The mITT population includes all randomized subjects who received at least one dose of assigned study drug. Analyses are performed according to randomized treatment assignment, not the treatment received. This analysis set will be used for all efficacy analyses and will be considered the primary analysis for the primary efficacy outcome measure.

6.3.2. Per Protocol (PP) Population

The PP population will include all subjects who met all inclusion/exclusion criteria, complied with the assigned study product, complied with the daily diary, and were followed up until resolution of symptoms, or completed 180 days without resolution of symptoms.

A subject is considered to be compliant with the assigned study product if he/she takes at least 75% of the scheduled doses through 28 days and does not receive additional nitazoxanide (defined as in Section 3.3) before their primary outcome is observed. A subject is compliant with the daily diary if he/she is missing no more than 1.5/7 days per week over the first 8 weeks (Day 1 through Day 60).

This analysis set will be used for all efficacy analyses and will be considered secondary to analyses conducted in the mITT population.

6.3.3. Safety Population

The safety population (grouped by actual treatment received) will include all subjects who are randomized, have received at least one dose of study treatment. This analysis set will be used for all safety analyses.

6.3.4. Immunogenicity Population

The immunogenicity population will include all randomized subjects who received at least one dose of assigned study drug and have at least one stool and/or serum immunoglobulin test result. This analysis set will be used for all immunogenicity analyses.

6.4. Covariates and Subgroups

As described in Section 4.4.3, the randomization of treatment assignments and the primary analysis will be performed as stratified by duration of symptoms, transplant type, and age range.

The protocol also defines formal subgroup analyses as exploratory outcome measures; however, the study was not powered to perform these subgroup analyses. Subgroup sensitivity analyses for the primary and secondary outcome measures will evaluate the treatment effect across the following subgroups:

- Additional nitazoxanide: Subjects that took additional nitazoxanide (defined as in Section 3.3) will be excluded from the analyses
- Chromaturia: Subjects with unsolicited self-reported chromaturia (discoloration of urine) will be excluded from the analyses.

Listing 22 and Listing 11 provide listings of subjects that reported chromaturia or took additional nitazoxanide, respectively.

6.5. Missing Data

All attempts were made to collect all data per protocol. Imputations will only be performed for missing daily diary data as it relates to the primary endpoint. Missing daily diary data for the primary endpoint will be handled as follows:

- Data that are missing after a subject has reached clinical resolution will not affect the primary time to event analysis and therefore will be ignored
- Subjects who drop out, are lost to follow-up, withdraw consent, or otherwise stop completing daily diary entries before clinical resolution will be censored on the day of their last completed diary
- Subjects with a gap in outcome data prior to clinical resolution will be handled depending on their last completed diary entry and their next completed diary entry:
    - If the last completed diary entry and the next completed diary entry have the same outcome (i.e., they are still symptomatic on both days or they have no symptoms on both days), then the gap will be imputed with the same outcome
    - If this imputation results in the subject being defined as having clinical resolution during this gap, their time to resolution will be the median of the interval
    - If the last completed diary entry and the next completed diary entry have different outcomes (i.e., the last one is symptomatic and the next one is asymptomatic, or vice versa), then the gap will be imputed with the symptomatic outcome (no resolution).

Table 3 provides summary statistics (n, mean, median, standard deviation, minimum, and maximum) of the number of imputed diary days per subject given the above imputation rules and the number of overall missing diary days per subject. The above method will be considered the primary imputation method for the primary endpoint. In addition, a sensitivity analysis on the primary endpoint will be conducted using worst case scenario for subjects who drop out, are lost to follow-up, withdraw consent, or otherwise stop completing

daily diary entries before clinical resolution. These subjects will be censored at 180 days (i.e., assuming resolution of symptoms occurred after Day 180). Listing 9 provides subject-level details for the number of diaries missed by week.

6.6. Interim Analyses and Data Monitoring

The Data and Safety Monitoring Board (DSMB) planned to review and discuss study data when 25% (N=40), 50% (N=80), and 75% (N=120) of patients completed Day 60 of the study. All planned DSMB reviews were to include descriptive summaries and were not intended to serve as formal interim analyses. Blinded and unblinded reports on safety data through Day 60, Norovirus infection clinical adverse outcome through Day 180 along with available clinical and virologic efficacy data and study product nitazoxanide retreatment data were expected to be reviewed at each study milestone.

At the time of this SAP, the study was stopped after 31 subjects enrolled due to enrollment challenges. Even though the study never reached the first milestone (N=40 subjects), the DSMB completed an unplanned electronic review of the Open and Closed Safety and Summary Reports on 02 November 2020.

The halting rules did not utilize any statistical criteria and no formal hypothesis testing occurred for the safety or efficacy review; therefore, no adjustment for multiple testing will be performed.

A final review meeting will be conducted 6 to 8 months after clinical database lock to review the cumulative unblinded safety and efficacy data for the study.

6.7. Multicenter Studies

Data will be pooled across all clinical sites. Center effects are not anticipated because the sites are using standardized procedures for product administration and assessment of safety and efficacy endpoints.

6.8. Multiple Comparisons/Multiplicity

There is only one primary endpoint. No adjustments for multiple testing are planned.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Table 9 will present a summary of the reasons that subjects were screened but not enrolled.

The composition of analysis populations, including reasons for subject exclusion, by treatment arm, is presented in Table 7.

The disposition of subjects in the study will be tabulated by treatment group (Table 6).

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

A listing of subjects who terminated from study follow-up or discontinued treatment and the reason will be included in Listing 2.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by deviation category, type, and treatment group for all subjects (Table 4). All subject-specific protocol deviations and non-subject specific protocol deviations will be included in Appendix 3 as data listings (Listing 3 and Listing 4, respectively).

8. EFFICACY EVALUATION

All primary and secondary efficacy analyses will be conducted in the mITT and PP populations. Data will be summarized by treatment group with a column for each treatment in the order (Nitazoxanide, Placebo) and will be annotated with the total population size relevant to that table/treatment. Subgroups with less than five subjects per treatment group will be excluded from efficacy tables and figures. All efficacy variables will be listed by site, treatment group and subject, and when appropriate, by visit number within subject (Listing 12, Listing 13, Listing 14, Listing 15, Listing 16, Listing 17, Listing 18, Listing 19, and Listing 22).

8.1. Primary Efficacy Analysis

The primary efficacy outcome measure is the time from randomization to initial clinical resolution of Norovirus for at least 48 hours, assessed through 180 days, in each study arm. Clinical resolution will be assessed from the daily diary by the subject and will be defined as in Section 3.3.

The protocol calls for a formal hypothesis test to compare nitazoxanide to placebo. The null hypothesis is that there is no difference in time until clinical resolution between study arms, with a two-sided alternative. A stratified Log-Rank test at the 5% two-sided level of significance was planned to test the hypothesis, however, due to early closure of the study, the number of subjects is too small to use a Log-Rank test. Instead, a stratified Cox proportional hazards model will be used to compare treatment to control through Day 180 with respect to time to clinical resolution. Stratification is based on acute versus chronic symptoms at baseline. No pediatric subjects were enrolled in the study and only one hematopoietic stem cell transplant subject was enrolled in the study; therefore, the transplant type and age range stratums will not be included in the final analysis.

The primary analysis will be performed in the mITT analysis population. Missing diary data will be imputed using the methods described in Section 6.5. The treatment hazard ratio estimate, 95% confidence interval and p-value from the likelihood ratio test will be presented (Table 16). The median time to clinical resolution and 95% confidence interval will be summarized by treatment arm and duration of symptoms. In addition, stratum-specific estimates of the treatment hazard ratio within each duration of symptoms strata will be presented. Kaplan-Meier curves for each treatment arm will be displayed in Figure 3. Figure 6 will present Kaplan-Meier curves for each treatment arm and duration of symptoms strata.

8.1.1. Supplemental and Sensitivity Analyses

The primary analysis will be repeated in the Per Protocol analysis population, where subjects who were not compliant with the diary and/or treatment will be excluded from the analysis. The tabular and graphical summaries described in the previous section will be replicated for this Per Protocol analysis (Table 16, Figure 4, and Figure 7).

Sensitivity analyses will be performed using the stratified Cox proportional hazards model on both the mITT population and PP population using the worst-case scenario imputation method for subjects who drop out, are lost to follow-up, withdraw consent, or otherwise stop completing daily diary entries before clinical resolution (Table 17). These subjects will be censored at 180 days. Kaplan-Meier curves for each treatment arm will be presented (Figure 5). Kaplan-Meier curves for each treatment arm and duration of symptoms strata will be displayed in Figure 8.

The primary analysis will be repeated on the mITT population using the subgroups defined in Section 6.4 (Table 18). A sensitivity analysis will be performed using the stratified Cox proportional hazards model on the mITT population with stratification based on subjects with less than 2 missing diaries per week versus

those with 2 or more missing diaries per week (Table 19). Kaplan-Meier curves for each treatment arm and diary compliance strata will be presented in Figure 9.

8.2. Secondary Efficacy Analyses

The secondary efficacy outcome measures are as follows:

- The time from randomization to first negative viral load through 180 days.
- The change in viral titer between Day 1 and Day 180.

The protocol calls for a Log-Rank test to compare time from randomization to first negative viral load through 180 days between the nitazoxanide treated group and the placebo group; however, due to early closure of the study, the number of subjects is too small to use a Log-Rank test. Number and percentage of subjects with positive viral load and geometric mean viral titer in positive subjects with 95% confidence intervals will be presented by test type, treatment group and study day in the mITT Population (Table 20). A stratified Cox proportional hazards model will be used to compare treatment to control through Day 180 with respect to time to first negative viral load. Stratification will be based on acute versus chronic symptoms at baseline. GII and GI test types will be analyzed independently.

The analysis will be conducted in both the mITT population and the PP population. The treatment hazard ratio estimate, 95% confidence interval and p-value from the likelihood ratio test will be presented for each test type (Table 21 and Table 22). The median time to clinical resolution and 95% confidence interval will be summarized by treatment arm and duration of symptoms for each test type. In addition, stratum-specific estimates of the treatment hazard ratio within each duration of symptoms strata will be presented for each test type. Kaplan-Meier curves for each treatment arm will be displayed in Figure 10, Figure 11, Figure 12 and Figure 13, for each test type in the mITT and PP populations. Figure 14 and Figure 15 will present Kaplan-Meier curves for each treatment arm and duration of symptoms strata for Norovirus GII and Norovirus GI test types, respectively, in the mITT population.

The analysis will be repeated on the mITT population using the subgroups defined in Section 6.4 for each test type (Table 23 and Table 24).

The change in viral titer between Day 1 and Day 180 will be assessed using analysis of covariance (ANCOVA) adjusting for baseline viral titer. The analysis will be conducted in both the mITT population and the PP population for both Norovirus GII and Norovirus GI test types. Table 25 and Table 26 will present the observed means and standard deviations of the change in viral titer between Day 1 and Day 180 for each treatment group and duration of symptoms strata for Norovirus GII and Norovirus GI test types, respectively. Levene's test and normality checks will be carried out to check if the assumptions of ANCOVA are met. If assumptions of ANCOVA have been met, the adjusted mean, standard error, and 95% confidence intervals will also be presented for each treatment group and duration of symptoms strata. The p-value for the test of between treatment differences will also be presented. If the assumptions of ANCOVA are not met, transformations of the change in viral titer variable may be utilized to correct any skewness in residuals or heterogeneity of the variances. If a transformation of the dependent variable is used, a footnote in the table will denote which transformation was used in the analyses. If the assumptions of ANCOVA cannot be met through transformation of the dependent variable, only the observed mean, standard deviation and 95% confidence intervals of the unadjusted change in viral titer between Day 1 and Day 180 will be reported. A forest plot will display the adjusted means and 95% confidence intervals of the change in viral titer between Day 1 and Day 180 for each treatment group and duration of symptoms strata for each test type (Figure 16, Figure 17, Figure 18 and Figure 19).

The ANCOVA analysis will be repeated on the mITT population using the subgroups defined in Section 6.4 for each test type (Table 27 and Table 28).

8.3. Exploratory Efficacy Analyses

The protocol calls for a Log-Rank test at the 5% two-sided level of significance for the following exploratory outcome measures:

- Time from randomization to initial clinical improvement in Norovirus disease through 28 and 180 days for at least 48 hours.
- Time from randomization to initial cessation of vomiting through Day 180 (recurrent vomiting will be considered disease recurrence unless determined to be due to another etiology [i.e. GVHD]).
- Time from randomization to subject report of no loss of appetite that is maintained for 48 hours through Day 180 (measure will be first time that the subject reports that they have no "loss of appetite" on their daily diary).
- Time from randomization to initial cessation of diarrhea through Day 180 classified by the Bristol Stool Chart as type 6 or 7 bowel movements (recurrent diarrhea will be considered disease recurrence unless determined to be due to another etiology [i.e. GVHD]).
- Time from randomization to 50% reduction in the amount of antimotility agents utilized by the subject through Day 180.

However, due to early closure of the study, the number of subjects is too small to use a Log-Rank test. Instead, a stratified Cox proportional hazards model will be used to compare treatment to control through Day 28 and/or Day 180. Stratification is based on acute versus chronic symptoms at baseline. No pediatric subjects were enrolled in the study and only one hematopoietic stem cell transplant subject was enrolled in the study; therefore, the transplant type and age range stratums will not be included in the final analysis.

The analysis will be performed in the mITT analysis population. The treatment hazard ratio estimate, 95% confidence interval and p-value from the likelihood ratio test will be presented for each event (Table 29). The median time to event and 95% confidence interval will be summarized by treatment arm and duration of symptoms. In addition, stratum-specific estimates of the treatment hazard ratio within each duration of symptoms strata will be presented. Kaplan-Meier curves for each treatment arm will be displayed in Figure 20, Figure 21, Figure 22, Figure 23, and Figure 24.

The protocol calls for two-sample t-tests to be used for the below outcome measures. However, due to early closure of the study, the number of subjects is too small to meet the normality assumptions of the t-test; therefore Wilcoxon-Mann-Whitney exact rank sum tests will be used to compare treatment to placebo through Day 28 and/or Day 180 in the mITT analysis population (Table 30) for the following outcome measures (defined in Section 3.3):

- Number of days of diarrhea through Days 28 and 180.
- Number of stools classified by the Bristol Stool Chart as type 6 or 7 bowel movements through Day 28.
- Number of days of IV hydration or total parenteral nutrition (TPN) therapy through Day 28.

The following patient-reported outcome measures will be assessed using ANCOVA adjusting for the baseline patient-reported measure:

- Change in patient-reported quality of life as measured by EuroQOL-5 (global) and IBSQOL (diarrhea specific) [adult] or Euro QOL-5 Peds (global) and PedsQL GI Module [children] from baseline to Day 180.
- Change in patient-reported physical function as measured by the NIH PROMIS Physical Function (Adult) Pediatric Global Health (Peds) from baseline to Day 180.
- Change in patient-reported emotional distress as measured by the NIH PROMIS Depression, Anxiety, Fatigue (Adult and Peds) from baseline to Day 180.
- Change in patient-reported gastrointestinal symptoms as measured by the NIH PROMIS GI (Adult and Peds) symptoms (6 of 8 subscales) from baseline to Day 180.

The analysis will be conducted in the mITT population. Table 31 and Table 32 will present the frequency of reported problems the EuroQOL-5 quality of life by dimension and study day for the nitazoxanide and placebo groups, respectively. Table 33 will present the observed means and standard deviations of the change in each patient-reported measure between baseline and Day 180 for each treatment group. Levene's test and normality checks will be carried out to check if the assumptions of ANCOVA are met. If assumptions of ANCOVA have been met, the adjusted mean, standard error, and 95% confidence intervals for each treatment group. The p-value for the test of between-treatment differences will also be presented. If the assumptions of ANCOVA are not met, transformations of the change in patient-reported measure variable may be utilized to correct any skewness in residuals or heterogeneity of the variances. If a transformation of the dependent variable is used, a footnote in the table will denote which transformation was used in the analyses for each patient-reported measure. If the assumptions of ANCOVA cannot be met through transformation of the dependent variable, only the observed mean, standard deviation and 95% confidence intervals of the unadjusted change in patient-reported measure and study day will be reported. The protocol also calls for pairwise contrasts between groups on the unadjusted change between baseline and subsequent timepoints and on adjusted change (controlling for baseline) using a mixed-design analysis of variance (ANOVA) model with all times, including baseline, as a repeated measures factor. However, due to early closure of the study, the number of subjects is too small to provide adequate power for any multiple comparison tests. Instead, Table 33 will present the observed means and standard deviations of the change in each patient-reported measure between baseline and Days 28, 60, and 120 for each treatment group. Since a single index is not currently possible for the EuroQOL-5 questionnaire, these results will not be included in Table 33. If ANCOVA assumptions are met, the adjusted mean, standard error, and 95% confidence intervals for each treatment group and study day will also be presented.

The effect of co-pathogens, as determined by the BioFire stool pathogen screen, on the primary outcome measure is presented in Table 34, where the presence or absence of co-pathogens will be represented as a binary covariate in the Cox proportional hazards model. If it is determined that subjects' co-pathogen status changes often throughout the study, the effect of co-pathogens will be a time-varying covariate instead of a binary covariate.

Time from randomization until clinical resolution of Norovirus symptoms for at least 48 hours through Day 180. Clinical resolution will be assessed from the daily diary by the subject and will be defined as cessation of vomiting and no stools classified by the Bristol Stool Chart as diarrhea (Type 6 or 7) from the total population compared to the subgroup of subjects who do not report chromaturia (discoloration of urine) based on unsolicited self-reporting is presented in Table 18.

The effect of co-pathogens, as determined by the BioFire stool pathogen screen, on the time from randomization to first negative viral load through 180 days is presented in Table 35 and Table 36 for Norovirus GII and Norovirus GI test types, respectively, where the presence or absence of co-pathogens will be represented as a binary covariate in the Cox proportional hazards model. If it is determined that subjects' co-pathogen status changes often throughout the study, the effect of co-pathogens will be a time-varying covariate instead of a binary covariate.

Time from the randomization to first negative viral load through 180 days and the change in viral titer between Day 1 and 180 from the total population compared to the subgroup of subjects who do not report chromaturia (discoloration of urine) based on unsolicited self-reporting will be presented in Table 23 and Table 24 for Norovirus GII and Norovirus GI test types, respectively .

Analyses of the following exploratory outcome measures are not covered in this SAP:

- Time to $\geq$ 1 log reduction in stool Norovirus genome copies
- Change in quantitative Norovirus load in the stool between Day 1 and Day 7, 14, 21, 28, 60, 120, and 180.
- Change in Norovirus sequence from Day 1 to Days 28 and 60.

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, subject 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, race, duration of symptoms, transplant type, and categorical age range will be presented by treatment group, overall and by site (Table 11, Table 12, Table 13, and Table 14). Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual subject listings (Appendix 3) will be presented for all demographics (Listing 6); pre-existing medical conditions (Listing 7); vital signs and oral temperature (Listing 27); and concomitant medications (Listing 32).

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 24.0 or higher.

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

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

9.1.2. Prior and Concomitant Medications

Summaries of medications that were started prior to dosing and continuing at the time of dosing, as well as any medications collected through visit 12 (Day 180) or early termination, whichever occurs first, will be presented by WHO Drug Levels 1 and 2 and treatment group (Table 115).

Individual subject listings will be presented for all concomitant medications (Listing 32).

9.2. Measurements of Treatment Compliance

The number of subjects who received any treatment and the number of subjects who received all scheduled treatments through Days 7, 14, 21, and 28 is presented by treatment group in Table 6. The number of subjects that received any additional nitazoxanide and additional nitazoxanide after Day 28 will also be included in the table. A subject is considered compliant with the assigned study product if they take at least 75% of the scheduled doses through 28 days and do not receive additional nitazoxanide before the primary outcome is observed. Table 10 provides the number of subjects compliant with study product, the mean cumulative number of pills taken and the mean percentage of pills taken for each treatment group at Days 7, 14, 21, and 28. A listing of treatment compliance by subject is presented in Listing 8.

9.3. Adverse Events

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

An overall summary of adverse events is presented in Table 49. Table 50 presents subject-level rates and differences between treatment groups for the following safety outcome measures:

- Incidence of unsolicited non-serious adverse events through 60 days (Day 60)
- Incidence of laboratory adverse events (WBC, Hemoglobin, Platelet count, Creatinine, Alkaline Phosphatase, ALT, AST, BUN, and Bilirubin) through 60 days (Day 60)
- Incidence of protocol-specified serious adverse events through 60 days (Day 60)
- Incidence of hospitalization through 60 days (Day 60)

Table 51 repeats these subject-level rates and differences between treatment groups for the subjects that do not report chromaturia.

9.3.1. Unsolicited Adverse Events

The proportion of subjects reporting at least one unsolicited adverse event will be summarized by MedDRA System Organ Class (SOC) and Preferred Term. Denominators for percentages are the number of subjects in the safety population.

Adverse events by subject will be presented in Listing 21.

The following summaries for unsolicited adverse events will be presented by MedDRA System Organ Class, Preferred Term, and treatment group:

- Summary of adverse events occurring in 5% of subjects (Table 52);
- Subject incidence and total frequency of adverse events over time by study phase with 95% CI (Treatment Phase, Longitudinal Phase) (Table 53, Table 54, and Table 55)
- Summary of severity and relationship to study product (Table 56, Table 57 , and Table 58);
- Summary of incidence and total frequency of related adverse events during the treatment phase (Days 1 – 28) (Table 59)
- Subject listing of serious adverse events (Table 60);
- Subject listing of non-serious adverse events of moderate or greater severity (Table 61);
- Bar chart of related adverse events by MedDRA SOC and severity (Figure 25);
- Bar chart of incidence of related adverse events by MedDRA SOC and maximum severity (Figure 26);

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

A subject listing of deaths and serious adverse events (Table 60) will be presented including Subject ID, Adverse Event Description, Adverse Event Onset Day and Duration, Reason Reported as an SAE, Severity, Relationship to Treatment, Alternate Etiology if not Related, and Outcome. A subject level listing of deaths including cause of death will be included in Listing 30.

9.5. Pregnancies

For any subjects in the Safety population who became pregnant during the study, every attempt was made to follow these subjects 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 33, Listing 34, Listing 35, Listing 36, and Listing 37).

9.6. Clinical Laboratory Evaluations

Safety laboratory parameters are defined in Section 4.5.3. Chemistry parameters include creatinine, alkaline phosphatase, AST, ALT, BUN, and total bilirubin. Hematology parameters include WBC, hemoglobin, and platelets. In addition, T-Cell subsets were also collected and include CD3 (CD3+), CD3/lymphocytes (CD3 + %), CD3 (CD3+), CD4/lymphocytes (CD4 + %), CD8 (CD8+), and CD8/lymphocytes (CD8 + %) and other hematology parameters (neutrophil, lymphocyte, eosinophil, monocyte, hematocrit, and mean corpuscular volume) were collected. The distribution of laboratory results by time point, treatment group, and maximum severity will be presented in Table 64, Table 65, Table 66, Table 67, Table 68, Table 69, and Table 70 for chemistry parameters and in Table 84, Table 85, Table 86, and Table 87 for hematology parameters. The distribution of abnormal laboratory results related to study treatment by time point, treatment group, and maximum severity will be presented in Table 71, Table 72, Table 73, Table 74, Table 75, Table 76, and Table 77 for chemistry parameters and in Table 88, Table 89, Table 90, and Table 91 for hematology parameters. Descriptive statistics including mean, standard deviation, median, minimum, and maximum values by time point, for each laboratory parameter, will be summarized in Table 78, Table 79, Table 80, Table 81, Table 82, and Table 83 for chemistry parameters and Table 92, Table 93, and Table 94 for hematology parameters. Additionally, descriptive statistics will be summarized in Table 95, Table 96, Table 97, Table 98, Table 99, Table 100, Table 101, Table 102, Table 103, Table 104, Table 105, and Table 106 for the T-Cell subset parameters and other hematology data that were not evaluated for abnormality.

Listing of abnormal laboratory results for chemistry and hematology parameters will be presented in Table 62 and Table 63, respectively. Listing 24 and Listing 25 will provide a complete listing of individual clinical laboratory results with applicable reference ranges. A complete listing of individual T-Cell subset results will be provided in Listing 26.

9.7. Vital Signs and Physical Evaluations

Vital sign measurements included weight, systolic blood pressure, diastolic blood pressure, respiration, pulse, and oral temperature. Vital signs were assessed at Day 1, Day 7, Day 14, Day 21, Day 28, Day 60, Day 120, and Day 180. Height was also measured at Day 1. Vital signs will be tabulated by visit and treatment group (Table 109, Table 110, Table 111, Table 112, Table 113, and Table 114). All vital signs will be listed by subject and time point in Listing 27.

Physical Examinations were performed at Day 1 and Day 28. The change in physical examination data from Day 1 will be summarized for each visit by treatment group for subjects in the Safety population (Listing 31).

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-subject listing of concomitant medication use will be presented (Listing 32). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group for the Safety Population (Table 115).

9.9. Other Safety Measures

Hospitalizations were collected as an outcome measure for the secondary objective and therefore were not reported as serious adverse events. Table 50 presents subject-level rates and differences between treatment groups for the incidence of hospitalization through 60 days. The protocol calls for the average number of days of hospitalization to be estimated and compared between treatment groups using a two-sample t-test. However, due to early closure of the study, the number of subjects is too small to meet the normality assumptions of the t-test; therefore Wilcoxon-Mann-Whitney exact rank sum tests will be used to compare the number of days of hospitalization between treatment and placebo through Day 28 and Day 180 in the Safety Population (Table 107). A listing of all hospitalizations is presented in Listing 28.

10. IMMUNOGENICITY

Summary statistics including the number of subjects with a valid result, geometric mean titer and 95% CI, median, minimum, and maximum will be provided by study day and treatment group for Norovirus-specific serum and stool IgA, IgM, and IgG in Table 37. In addition, geometric mean fold-rise and proportion of responders (defined as four-fold or greater increase from baseline) with 95% confidence intervals will be displayed in Table 38 Confidence intervals for the proportion of responders will be Wilson score two-sided 95% CIs. Table 37 and Table 38 will also provide summaries for Total Serum IgG and the ratio of Norovirus-specific IgG to Total IgG for each study day and treatment group.

The change in Norovirus-specific serum and stool IgA, IgM, and IgG between Day 1 and Day 28 and Day 1 and Day 60 will be assessed using analysis of covariance (ANCOVA) adjusting for baseline assay value. The analysis will be conducted in the mITT population. Table 39 will present the observed means and standard deviations of the change in Norovirus-specific serum and stool IgA, IgM, and IgG between Day 1 and Day 28 and Day 1 and Day 60 for each treatment group. Levene's test and normality checks will be carried out to check if the assumptions of ANCOVA are met. If assumptions of ANCOVA have been met, the adjusted mean, standard error, and 95% confidence intervals will also be presented for each treatment group. The p-value for the test of between treatment differences will also be presented. If the assumptions of ANCOVA are not met, transformations of the change in assay variable may be utilized to correct any skewness in residuals or heterogeneity of the variances. If a transformation of the dependent variable is used, a footnote in the table will denote which transformation was used in the analyses. If the assumptions of ANCOVA cannot be met through transformation of the dependent variable, only the observed mean, standard deviation and 95% confidence intervals of the unadjusted change in Norovirus-specific serum and stool IgA, IgM, and IgG between Day 1 and Day 28 and between Day 1 and Day 60 will be reported.

A mixed effects model will be used to compare the change in each Norovirus-specific serum and stool IgA, IgM, and IgG between nitazoxanide and placebo for each assay. Norovirus-specific serum and stool IgA, IgM, and IgG measured on study days 1, 28 and 60 will be included in the mixed effects model. Below the mixed effects model for Norovirus-specific serum IgA is described. Analyses for each assay type will be performed in a similar manner.

The mean Norovirus-specific serum IgA with 95% confidence intervals will be displayed graphically for each time point for each treatment group. If a linear relationship between Norovirus-specific serum IgA and time is observed for both groups, then a model that makes use of this simplifying assumption will be used. Letting Y denote Norovirus-specific serum IgA, t denote the time point (study day), and i be a subject index, and letting *treatment*=1 for those in the nitazoxanide group and *treatment*=0 for those in the placebo group, we will model serum IgA as:

$$Y_{it} = \beta_0 + \beta_1 t + \mu_i + \alpha_i t + \beta_2 treatment + \beta_3 treatment \cdot t + \epsilon_{it},$$

If the relationship is nonlinear, then a transformation (e.g. log transformation) may be applied, or we will fit the following model, which relaxes the linearity assumption. Let $1_{[t=k]}$ denote an indicator variable taking the value one when t=k and zero otherwise. Let u_i denote the random intercept for subject i and let α_i denote the random slope for subject i, and assume these random effects are normally distributed with mean zero. Then without assuming linearity, the serum IgA for subject i at time t can be modeled as:

$$Y_{it} = \beta_0 + \mu_i + \alpha_i t + \beta_1 \cdot treatment + \beta_2 1_{[t=28]} + \beta_3 1_{[t=28]} \cdot treatment + \beta_4 1_{[t=60]} + \beta_5 1_{[t=60]} \cdot treatment + \epsilon_{it},$$

The error terms, ϵ_{it}, are assumed to be independent and normally distributed with constant variance and mean zero. If residual plots indicate that variance is not constant and/or the errors are not normally distributed, transformations (e.g., the log transformation of the response) will be considered. Choice of covariance structures for the random effects (e.g., compound symmetric and autoregressive), will be explored.

In this model, the expected serum IgA for the placebo group on Day 1 is β_0, and on Day 28 (t=28) is $\beta_0 + \beta_2$. Therefore, the expected change from time Day 1 to Day 28 is β_2 for the placebo group. The expected serum IgA for the nitazoxanide group on Day 1 is $\beta_0 + \beta_1$, and on Day 28, it is $\beta_0 + \beta_1 + \beta_2 + \beta_3$. Therefore, the expected change for the nitazoxanide group from Day 1 to Day 28 is $\beta_2 + \beta_3$. Thus, the difference in rate of change in Norovirus-specific serum IgA from Day 1 to Day 28 between nitazoxanide and placebo groups is, on average, β_3. The interpretation for parameter β_5 is similar.

The analyses will be performed on the Immunogenicity population. Table 40 will present the coefficient estimates for the mixed effects model for the Norovirus-specific serum IgA assay. Table 41, Table 42, Table 43, Table 44, and Table 45 will present the coefficient estimates for the mixed effects models for the remaining assay types.

The relationship between change in total lymphocyte count between Day 1 and 180 and the day of initial clinical resolution of symptoms will be evaluated using Pearson correlations. A Fisher's Z-transformation will be applied to the Pearson correlations in both the nitazoxanide and placebo groups. These will then be compared using a Z-test and the p-value will be reported along with the Pearson correlations and 95% confidence intervals in Table 46. The following relationships will also be evaluated in Table 46:

- Change in T cell subsets between Day 1 and 180 and the day of initial clinical resolution of symptoms.
- Change in total lymphocyte count between Day 1 and 180 and the first day of undetectable quantitative Norovirus PCR (see viral load in Section 3.3).
- Change in T cell subsets between Day 1 and 180 and the first day of undetectable quantitative Norovirus PCR (see viral load in Section 3.3).

Similarly, Table 47 will evaluate the following relationships:

- Change in Norovirus-specific serum and stool IgA, IgM, and IgG from Day 1 to Day 28 and the day of initial clinical resolution of symptoms.
- Change in Norovirus-specific serum and stool IgA, IgM, and IgG from Day 1 to Day 60 and the day of initial clinical resolution of symptoms.
- Change in Norovirus-specific serum and stool IgA, IgM, and IgG from Day 1 to Day 28 and the first day of undetectable quantitative Norovirus PCR (see viral load in Section 3.3).
- Change in Norovirus-specific serum and stool IgA, IgM, and IgG from Day 1 to Day 60 and the first day of undetectable quantitative Norovirus PCR (see viral load in Section 3.3).

All immunogenicity variables will be listed by treatment group, subject, and visit in Listing 20 and Listing 21 .Total lymphocyte counts, and T-Cell subsets will be listed in Listing 23 and Listing 24, respectively.

11. OTHER ANALYSES

The protocol calls for a Log-Rank test at the 5% two-sided level of significance for the following outcome measures:

- Time to allograft rejection as per each center team.
- Time to graft loss as reported to UNOS.
- Time to death.
- Time to withdrawal from the study because of intolerance or drug related adverse events.

However, due to early closure of the study, the number of subjects is too small to use a Log-Rank test. Instead, a stratified Cox proportional hazards model will be used to compare treatment to control through Day 180. Stratification is based on acute versus chronic symptoms at baseline. No pediatric subjects were enrolled in the study and only one hematopoietic stem cell transplant subject was enrolled in the study; therefore, the transplant type and age range stratums will not be included in the final analysis.

The analysis will be performed in the mITT analysis population. The treatment hazard ratio estimate, 95% confidence interval and p-value from the likelihood ratio test will be presented for each event (Table 108). The median time to event and 95% confidence interval will be summarized by treatment arm and duration of symptoms. In addition, stratum-specific estimates of the treatment hazard ratio within each duration of symptoms strata will be presented. Kaplan-Meier curves for each treatment arm will be displayed in Figure 27, Figure 28, Figure 29, and Figure 30. A listing of graft loss and rejection is presented in Listing 29 and a listing of deaths is presented in Listing 30.

The primary analysis will be repeated on the mITT population using secretor status as defined by phenotype and genotype, separately (Table 48). Individual secretor status data is presented in Listing 19.

12. REPORTING CONVENTIONS

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

13. TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures and listings or R version 4.1.1 or higher.

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

14.1. Changes in the Conduct of the Study

14.1.1. Protocol Amendments

The first subject enrolled on protocol version 2.0. Subjects were also enrolled on protocol version 3.0. Substantive changes between these protocol versions are summarized below.

- Day 28 Visit will not reflect completion of treatment phase as subject will have to take the final dose after the visit. Treatment phase description was updated to reflect number of doses.
- The following stool related exploratory outcome measures and urine sensitivity outcome measures were added:
  - The effect of co-pathogens, as determined by the BioFire stool pathogen screen, on the primary outcome measure.
  - Time from randomization until initial clinical resolution of Norovirus symptoms for at least 48 hours through Day 180. Clinical resolution will be assessed from the daily diary by the subject and will be defined as cessation of vomiting and no stools classified by the Bristol Stool Chart as diarrhea (Type 6 or 7) from the total population compared to the subgroup of subjects who do not report chromaturia (discoloration of urine) based on unsolicited self-reporting.
  - Incidence of unsolicited non-serious adverse events (see section 9 for details) through 60 days, laboratory adverse events (WBC, Hemoglobin, Platelet count, Creatinine, Alkaline Phosphatase, ALT, AST, BUN and Bilirubin) through 60 days, protocol-specified serious adverse events (see section 9 for details) through 60 days, and Hospitalization through 60 days from the total population compared to the subgroup of subjects who do not report chromaturia (discoloration of urine) based on unsolicited self-reporting.
  - Time from the randomization to first negative viral load through 180 days and the change in viral titer between Day 1 and 180 from the total population compared to the subgroup of subjects who do not report chromaturia (discoloration of urine) based on unsolicited self-reporting.
- Addition of a $\pm$ 3-day window for the Study Day 35 call.

14.1.2. Study Product Administration

One site (University of Nebraska) received multiple kits representing one study product and no kits of the other study product when it ordered study product from the DMID Clinical Materials Services contractor. Due to this imbalance, the online randomization module in Advantage eClinical would have prevented randomization if it was attempted. To resolve the issue, the site was instructed to order additional kits, although they described their inventory as sufficient. The site was informed a second time that the number of kits they had on-site were insufficient and they would not be able to randomize unless they ordered more kits. The site subsequently agreed to order additional kits. This communication was considered by the SDCC to meet the definition of an accidental partial unblinding as it could be inferred that all the kits on-hand were identical. To address the issue, the MOP was updated to instruct sites to always order a minimum number of kits in addition to always maintaining a number of kits on-site. No changes to planned analyses were made in response to this situation.

14.1.3. Daily Diary Completion Time

Subjects were instructed to complete their daily diary at the same time each day. During manual review of the data, it was discovered that subjects had entry dates with morning diary times and/or diary times that were <12 hours from their previous entry's diary time. Given the inconsistencies in the timing of the daily diary entries, it is difficult to know if subjects were recording information for the previous study day or the prior 24 hours. For diary entries that are <12 hours apart, it is likely that information has been duplicated. The analyses assume that the data reflected in each diary is for the date of diary completion; however, this is a limitation that was not able to be resolved during the study. The number of diaries completed in pre-specified windows (12pm – 6am, 6pm – 12am, 12am – 6am, and number completed less than 12 hours after previous diary completed) is provided in Listing 10.

14.2. Changes in Planned Analyses

It was originally planned that the study would enroll 160 subjects allowing for larger sample statistical methods to be used; however, due to early closure of the study only 31 subjects enrolled. Therefore, it is anticipated that many of these tests will no longer be valid. Many of the analyses from the protocol have been updated to employ small sample techniques and will be primarily descriptive.

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16. 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 Efficacy/Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 1: Schedule of Study Procedures

[Implementation Note: Include a graphic display of the frequency and timing of efficacy and safety measures including visit numbers. The schedule of procedures from the protocol may be excerpted and included here, as appropriate.]

Phase	Treatment Phase					Longitudinal Monitoring Phase								
Procedure	Screen/ Enroll/ Day 1	Day 7 (±3 d)	Day 14 (±3 d)	Day 21 (±3d)	Day 28 (+3 d)	Day 35	Day 53 (± 7d)	Day 60 (±14 d)	Day 113 (± 7d)	Day 120 (±14 d)	Day 173 (± 7d)	Day 180 (±14 d)	Unscheduled Visit	Early Termination visit
Visit	01	02	03	04	05	06	07	08	09	10	11	12		
Consent[1]	X													
Urine Pregnancy[2]	X													
WBC, TLC, Hb, Platelets [3#₱]	4 mL[₱]	4 mL[3]			4 mL[3]							4 mL[3]		4 mL[3]
Creatinine, Alk Phos, AST, ALT, BUN, Bilirubin.[3€₱]	4.5 mL[₱]	4.5 mL[3]			4.5 mL[3]							4.5 mL[3]		4.5 mL[3]
T-Cell Subsets[3]	4 mL											4 mL		4 mL
Pill Count		X	X	X	X			X[10]						
Vital Signs*	X	X	X	X	X			X		X		X	X	X
Medical History	X													
Physical Exam	X				X									
Inquiry about hospitalization since last Assessment		X	X	X	X	X		X		X		X		X
Stool for Pathogen Screen[¥]	X	X[7]	X[7]	X[7]	X[7]			X[7]		X[7]		X[7]	X[7]	X[7]
Stool Norovirus Testing	X[8¶]	X[¶]	X[¶]	X[¶]	X[8¶]			X[8¶]		X[¶]		X[¶]	X[¶]	X[¶]
Stool Ig Study	X		X[¶]		X			X		X[¶]		X[¶]		X[¶]
Serum Ig Study	10 mL				10 mL			10 mL				10 mL[¶]		10[¶] mL
Buccal Swab/Saliva Collection	X													
Randomization	X													
Nitazoxanide PK[4]		4.5 mL		4.5 mL										

Phase	Treatment Phase					Longitudinal Monitoring Phase								
Procedure	Screen/ Enroll/ Day 1	Day 7 (±3 d)	Day 14 (±3 d)	Day 21 (±3d)	Day 28 (+3 d)	Day 35	Day 53 (± 7d)	Day 60 (±14 d)	Day 113 (± 7d)	Day 120 (±14 d)	Day 173 (± 7d)	Day 180 (±14 d)	Unscheduled Visit	Early Termination visit
Nitazoxanide or placebo[5]	X	X	X	X	X									
Return residual medication					X									X
Review concomitant medications	X	X	X	X	X	X		X		X		X		X
Assess for adverse events		X	X	X	X	X		X					X	X
Administer Detailed PROs Packet	X				X			X		X		X		X
Administer Weekly Packet	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Daily Diary[6]		X	X	X	X			X		X		X	X	X
Phone Call for Status Update						X	X		X		X			
Phone Call for Appt Reminder							X		X		X			
Total Blood Volume	22.5 mL	13 mL	--	4.5 mL	18.5 mL	--	--	10 mL	--	--	--	22.5 mL	--	22.5 mL

[1]Consent/Assent must be obtained from eligible subjects, consistent with local IRB policy for consent and assent of subjects and must be obtained prior to any study procedures being performed

[2] Urine pregnancy test will be obtained from women of childbearing potential, results of test must be known and negative prior to dosing.

[3]Locally performed assay; values obtained within 7 days of the study visit, if obtained for clinical indication, can be utilized during the treatment phase and within 14 days of the study visit for the longitudinal monitoring phase. T cell subset will be drawn unless CBC shows an ALC<100.

[4] The PK specimen on Day 7 will be collected 1-4 hours after the subject takes the study dose and on Day 21 will be a pre-dose trough and will be drawn only in subjects consenting to this optional assessment.

[5] Nitazoxanide or placebo kit will be provided to the subject. Study drug (Nitazoxanide or placebo) given BID for 28 days.

[6] Diary recorded once a day during the treatment phase and once a day during the longitudinal monitoring phase. Copies of completed pages are collected at each study visit. One pack give an enrollment and additional copies provided at Day 28.

[7] Stool for pathogen screen will not be performed for formed stool except on Day 1 and 180. An aliquot will be retained for later testing if indicated. Norovirus testing includes quantitative viral load at all time points.

[8] Sequencing at selected time points.

[10]Day 60 pill count only needs to be conducted if the dosing was not completed and medications returned during Study Day 28.

[§] If diarrhea recurs after stopping therapy, would have subject provide a stool specimen for pathogen screen and Norovirus PCR; therapy is at the discretion of the site.

[¥] The sample must have been produced within 24 hours of the visit and if it exceeds 24 hours it must be disposed. After collection in the stool hat, the subjects can wipe down and disinfect the outside of the container and place it in a bag for transport then refrigerate until they come to their visit with the research staff. Subjects would be encouraged to provide another sample within the visit window and if not, rectal swab may be used for all assays related to stool collection.

*Vital Signs include weight, Blood Pressure, Respiration, Pulse, Temperature and Height. Height is only measured at Screening/Enrollment/Baseline visit.

[#]Derived from Complete Blood Count.

[€]Derived from Complete Metabolic Panel.

[¶]Specimen also stored for future use.

[₱]Must be within 3 days of enrollment

9.7.1 Sample Size

Table 2: Sample Size/Probability Estimates

		Proportion Receiving Additional Treatment in the Placebo Group						
		0%	5%	10%	15%	20%	25%	30%
Proportion re-treated in the nitazoxanide Group	0%	91.3%	91.6%	91.7%	91.6%	91.8%	92.0%	92.3%
	5%	91.4%	91.5%	91.6%	91.2%	91.2%	91.8%	92.5%
	10%	-	91.5%	92.0%	91.2%	91.8%	91.2%	92.2%
	15%	-	-	90.7%	90.7%	91.0%	91.6%	91.8%
	20%	-	-	-	87.3%	87.1%	87.0%	87.7%
	25%	-	-	-	-	74.0%	73.9%	75.2%
	30%	-	-	-	-	-	40.0%	40.9%

10.2 Protocol Deviations

Table 3: Missing Diary Days by Treatment Group

Diary Days	Statistic (days/subject)	Nitazoxanide 500 mg (N = X)	Placebo (N = X)	All Subjects (N = X)
Imputed [a]	n	x	x	x
	Mean	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Standard Deviation	xx.x	xx.x	xx.x
	Minimum	x	x	x
	Maximum	x	x	x
Total Missing [b]	n	x	x	x
	Mean	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Standard Deviation	xx.x	xx.x	xx.x
	Minimum	x	x	x
	Maximum	x	x	x

N=Number of subjects enrolled.
n = Number of subjects with imputed/missing diary days.
[a] Includes subjects with imputed diary days per imputation rules given in Section 9.7.2.2.
[b] Includes subjects with any missing diary days

Table 4: Distribution of Protocol Deviations by Category, Type, and Treatment Group

Category	Deviation Type	Nitazoxanide 500 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility /enrollment	Any type						
	Did not meet inclusion criterion	x	x	x	x	x	x
	Met exclusion criterion						
	ICF not signed prior to study procedures						
	Other						
Treatment administration schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Missed treatment administration						
	Delayed treatment administration						
	Other						
Follow-up visit schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Other						
Protocol procedure/ assessment	Any type						
	Incorrect version of ICF signed						
	Blood not collected						
	Urine not collected						
	Stool not collected						
	Other specimen not collected						
	Too few aliquots obtained						
	Specimen result not obtained						
	Required procedure not conducted						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Specimen temperature excursion						
	Other						
Treatment administration	Any type						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Other						
Blinding policy/ procedure	Any type						
	Treatment unblinded						
	Other						

N=Number of subjects in the Safety Population

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 5: Laboratory Adverse Event Grading Scale

Blood, Serum, or Plasma Chemistries[1]	**Reference Range**[2]	**LO/HI/N**[3]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Creatinine (mg/dL)		HI	>ULN - 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 x ULN
Blood Urea Nitrogen (BUN, mg/dL)		HI	>ULN - 26	27 - 31	>31
Alkaline phosphatase (U/L)		HI	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 x ULN
AST (U/L)		HI	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 x ULN
ALT (U/L)		HI	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 x ULN
Bilirubin, serum total (mg/dL)		HI	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 x ULN
Hematology	**Reference Range**[2]	**LO/HI/N**[3]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Hemoglobin (g/dL)		LO	<LLN – 10.0	<10.0 – 8.0	<8.0
White Blood Cell Count (WBC, K/CUMM)		HI	>ULN - 15.00	15.00 - 20.00	>20.00
		LO	<LLN – 3.0	<3.0 – 2.0	<2.0
Platelets (K/CUMM)		LO	<LLN - 75	<75 - 50	<50
Other Laboratory Parameters		LO/HI	Test result is associated with a mild sign or symptom.	Test result requires minimal, local or non-invasive intervention.	Test result requires an invasive medical or surgical intervention, or change in study dosing outside of the protocol defined dosing or discontinuation from the study treatment, or addition of new medication.

[1] Depending upon the lab used, references ranges, eligibility ranges and grading may be split out by sex and/or age.
[2] Reference range of individual study site laboratory
[3] High, Low, Not Graded
ULN – upper limit of normal; LLN – lower limit of normal

14.1.1 Disposition of Subjects

Table 6: Subject Disposition by Treatment Group

Subject Disposition	Nitazoxanide 500 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Enrolled/Randomized	x	100	x	100	x	100
Received Any Treatment	x	x.x	x	x.x	x	x.x
Received All Scheduled Treatments through Day 7[b]	x	x.x	x	x.x	x	x.x
Received All Scheduled Treatments through Day 14[b]						
Received All Scheduled Treatments through Day 21[b]						
Received All Scheduled Treatments through Day 28[b]						
Received any additional Nitazoxanide						
Received additional Nitazoxanide after Day 28						
Completed Study Day 60						
Completed Study Day 120						
Completed All Blood Draws[c]						
Completed All Stool Collections[d]						
Completed Follow-up (Study Day 180)[b]						
Terminated Early [b]						
Death						
Lost to Follow-Up						
Voluntary Withdrawal by Subject						
Withdrawal by Investigator						
Termination of Site/Study by Sponsor						
Other						

N = Number of subjects enrolled.
[a] Subjects are included if they have data indicating the study treatment was distributed and at least one pill count completed.
[b] Refer to Section 16.2.1 for reasons subjects discontinued or terminated early.
[c] Blood draws for serum Ig assays.
[d] Stool or rectal swabs collected for virus detection and stool for Norovirus specific Ig assays.

Table 7: Analysis Populations by Treatment Group

[Implementation Note: The reasons listed here should match the SAP text that describes who will be excluded from analyses. Although subjects may meet multiple criteria for exclusion, they should be counted under only one reason for exclusion in this table. Priority for assigning reasons for exclusions will be defined in the SAP text.]

Analysis Populations	Reason Subjects Excluded	Nitazoxanide 500 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
Modified Intention-to-Treat Population	Any Reason	x	xx	x	xx	x	xx
	Found to be ineligible at baseline						
	Did not receive at least one dose of study product						
Per Protocol Population	Any Reason						
	Found to be ineligible at baseline						
	Received less than 75% of scheduled doses through 28 days						
	Received additional Nitazoxanide 500 mg before primary outcome observed						
	Missed more than 1.5/7 days per week of the daily diary through 8 weeks (through Day 60)						
	Did not complete follow up						
Safety Population	Any Reason						
	Did not receive at least one dose of study product						
	Do not have a safety assessment						
Immunogenicity Population	Any Reason						
	Did not receive at least one dose of study product						
	Did not have at least one stool or serum immunoglobulin test result						

N=Number of subjects enrolled.
Note: Subjects who were excluded for more than one reason are only counted once. Reason excluded is prioritized as follows: ineligible at baseline, treatment compliance, additional Nitazoxanide 500 mg, diary compliance, and did not complete follow-up.

Table 8: Dates of First Treatment by Site and Treatment Group

[Implementation Note: Each site that enrolled subjects will have columns for Nitazoxanide 500 mg and placebo treatment groups.]

Site	Treatment Group	Date of First Dose						
		OCT2018-DEC2018	JAN2019-MAR2019	APR2019-JUN2019	…	…	…	JAN2021-MAR2021
Site 1	Nitazoxanide 500 mg (N = X)	x	x	x	x	x	x	x
	Placebo (N = X)							
	All Subjects (N = X)							
Site 2	Nitazoxanide 500 mg (N = X)							
	Placebo (N = X)							
	All Subjects (N = X)							
(Continue for All Sites that Enrolled Subjects)								

N = Number of subjects enrolled.

Table 9: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	100
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

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

Table 10: Treatment Compliance by Study Day and Treatment Group, Safety Population

Summary	Nitazoxanide 500 mg (N=X)					Placebo (N=X)				
	Visit 2 Day 7	Visit 3 Day 14	Visit 4 Day 21	Visit 5 Day 28	Final Pill Count [a]	Visit 2 Day 7	Visit 3 Day 14	Visit 4 Day 21	Visit 5 Day 28	Final Pill Count [a]
Number of Subjects Completing Visit	x	x	x	x	x	x	x	x	x	x
Number of Subjects Compliant with Study Treatment	x	x	x	x	x	x	x	x	x	x
Mean Cumulative Number of Pills Taken	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Mean Percentage of Pills Taken	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x

N = Number of subjects in the Safety Population.
Note: To be considered compliant at a visit, subjects must have taken at least 75% of their expected pills. Compliance for final pill count requires subjects take at least 42 pills.
[a] Final pill count will include Day 28 and Day 60 pill counts. Subjects with pill counts at both visits will use the Day 60 pill count as the final pill count.

14.1.2 Demographic Data by Study Group

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group

Variable	Characteristic	Nitazoxanide 500 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx
	Female						
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino						
	Not Reported						
	Unknown						
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx
	Asian						
	Native Hawaiian or Other Pacific Islander						
	Black or African American						
	White						
	Multi-Racial						
	Unknown						
Duration of Symptoms	Acute (less than 14 days)	x	xx	x	xx	x	xx
	Chronic (14 days or greater)						
Transplant Type	Solid organ	x	xx	x	xx	x	xx
	Hematopoietic Stem Cell Transplant						
Age Range	Pediatric (12-17 years)	x	xx	x	xx	x	xx
	Adult (≥ 18 years)						

N = Number of subjects enrolled.

Tables with similar format:

Table 12: Summary of Categorical Demographic and Baseline Characteristics by Site

[Implementation Note: Treatment Groups will be replaced with Site Names.]

Table 13: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group

Variable	Statistic	Nitazoxanide 500 mg (N=X)	Placebo (N=X)	All Subjects (N=X)
Age	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x

N = Number of subjects enrolled.

Tables with similar format:

Table 14: Summary of Continuous Demographic and Baseline Characteristics by Site

[Implementation Note: Treatment Groups will be replaced with Site Names.]

14.1.3 Prior and Concurrent Medical Conditions

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

MedDRA System Organ Class	Nitazoxanide 500 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx
[SOC 1]						
[SOC 2]						

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

14.2.1 Efficacy/Immunogenicity Response Tabular Summaries by Measure, Treatment and Time Point

Table 16: Time to Initial Clinical Resolution by Treatment Group and Duration of Symptoms

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable. If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses."

Analysis Population	Treatment Group	Duration of Symptoms	n	Median Time to Initial Clinical Resolution		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
mITT Population	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.x	x.x, x.x	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.x	x.x, x.x	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			
Implementation note: Repeat for the Per Protocol Population.								

N = Number of subjects in the specified treatment group, duration of symptoms strata, and analysis population.
n = Number of subjects with initial clinical resolution of symptoms.
Note: HR is the ratio of the hazard of initial clinical resolution in each treatment group estimated from the Cox model. The ratio is Nitazoxanide 500 mg to Placebo.
HR for the 'Any Duration' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the likelihood ratio test.

Additional table with similar format:

Table 17: Time to Initial Clinical Resolution by Treatment Group and Duration of Symptoms: Worst Case Scenario Sensitivity Analysis

Table 18: Time to Initial Clinical Resolution by Treatment Group and Duration of Symptoms: Subgroup Sensitivity Analysis – mITT Population

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable. If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses."

Subgroup	Treatment Group	Duration of Symptoms	n	Median Time to Initial Clinical Resolution		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
Additional Nitazoxanide 500 mg[a]	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.x	x.x, x.x	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.x	x.x, x.x	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			
Chromaturia[b]	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.x	x.x, x.x	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.x	x.x, x.x	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			

N = Number of subjects in the specified treatment group, subgroup, and duration of symptoms strata.
n = Number of subjects with initial clinical resolution of symptoms.
[a] Subjects that took additional Nitazoxanide 500 mg are excluded from the analyses.
[b] Subjects with unsolicited self-reported chromaturia (discoloration of urine) are excluded from the analyses.
Note: HR is the ratio of the hazard of initial clinical resolution in each treatment group estimated from the Cox model. The ratio is Nitazoxanide 500 mg to Placebo.
HR for the 'Any Duration' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the likelihood ratio test.

Table 19: Time to Initial Clinical Resolution by Treatment Group and Diary Compliance – mITT Population

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable. If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses."

Treatment Group	Diary Compliance	n	Median Time to Initial Clinical Resolution		HR	
			Estimate	95% CI	Estimate	95% CI
Nitazoxanide 500 mg (N=X)	Missing < 2 per week	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
Placebo (N=X)		x	x.x	x.x, x.x		
Nitazoxanide 500 mg (N=X)	Missing >= 2 per week	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
Placebo (N=X)		x	x.x	x.x, x.x		

N = Number of subjects in the specified treatment group and diary compliance strata.
n = Number of subjects with initial clinical resolution of symptoms.
Note: HR is the ratio of the hazard of initial clinical resolution in each treatment group estimated from the Cox model. The ratio is Nitazoxanide 500 mg to Placebo.

Table 20: Summary of Virologic Improvement by Test Type, Treatment Group, and Study Day – mITT Population

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable. If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses."

		Nitazoxanide 500 mg (N=XX)					Placebo (N=XX)				
Test Type	Summary	Visit 1 Day 1	Visit 5 Day 28	Visit 8 Day 60	Visit 10 Day 120	Visit 12 Day 180	Visit 1 Day 1	Visit 5 Day 28	Visit 8 Day 60	Visit 10 Day 120	Visit 12 Day 180
Norovirus GII	Number of Subjects with Positive Viral Load	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
	Geometric Mean Viral Titer in Positive Subjects (95% CI)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)
Norovirus GI	Number of Subjects with Positive Viral Load	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
	Geometric Mean Viral Titer in Positive Subjects (95% CI)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)	x.x (x.x,x.x)

N = Number of subjects in the mITT population. Subjects will only be included in the denominators if they have a valid result for the specified test type at the given visit.
n = Number of subjects with positive viral load for the specified test type at the given visit.

Table 21: Time to First Negative Viral Load by Treatment Group and Duration of Symptoms – Norovirus GII

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable." If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses.

Analysis Population	Treatment Group	Duration of Symptoms	n	Median Time to First Negative Viral Load		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
mITT Population	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			
Implementation note: Repeat for the Per Protocol Population.								

N = Number of subjects in the specified treatment group, duration of symptoms strata, and analysis population with positive Norovirus GII test results at baseline.
n = Number of subjects with first negative Norovirus GII viral load test result.
Note: HR is the ratio of the hazard of first negative Norovirus GII viral load in each treatment group estimated from the Cox model. The ratio is Nitazoxanide 500 mg to Placebo.
HR for the 'Any Duration' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the likelihood ratio test.

Table with similar format:

Table 22: Time to First Negative Viral Load by Treatment Group and Duration of Symptoms – Norovirus GI

Table 23: Time to First Negative Viral Load by Treatment Group and Duration of Symptoms: Subgroup Sensitivity Analysis – Norovirus GII, mITT Population

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable." If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses.

Subgroup	Treatment Group	Duration of Symptoms	n	Median Time to First Negative Viral Load		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
Additional Nitazoxanide 500 mg[a]	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			
Chromaturia[b]	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			

N = Number of subjects in the specified treatment group, subgroup, and duration of symptoms strata with positive GII test results at baseline.
n = Number of subjects with first negative GII viral load test result.
[a] Subjects that took additional Nitazoxanide 500 mg are excluded from the analyses.
[b] Subjects with unsolicited self-reported chromaturia (discoloration of urine) are excluded from the analyses.
Note: HR is the ratio of the hazard of first negative GII viral load in each treatment group estimated from the Cox model. The ratio is Nitazoxanide to Placebo.
HR for the 'Any Duration' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the likelihood ratio test.

Table with similar format:

Table 24: Time to First Negative Viral Load by Treatment Group and Duration of Symptoms: Subgroup Sensitivity Analysis – Norovirus GI, mITT Population

Table 25: Change in Viral Titer between Day 1 and Day 180 by Treatment Group and Duration of Symptoms – Norovirus GII

[Implementation Note: If a transformation of the dependent variable is used, a footnote in the table will denote which transformation was used in the analyses. If the assumptions of ANCOVA cannot be met, only the observed mean, standard deviation and 95% confidence intervals of the unadjusted change in viral titer between Day 1 and Day 180 will be reported. If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable." If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses.]

Analysis Population	Treatment Group	Duration of Symptoms	n	Observed Mean	Standard Deviation	Adjusted Mean	Standard Error	95% CI	P-value
mITT Population	Nitazoxanide 500 mg (N=X)	Acute (Baseline Mean = xx.x)	x	x.x	x.x	x.x	x.x	x.x, x.x	---
	Placebo (N=X)		x	x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N=X)	Chronic (Baseline Mean = xx.x)	x	x.x	x.x	x.x	x.x	x.x, x.x	---
	Placebo (N=X)		x	x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N=X)	Any Duration (Baseline Mean = xx.x)	x	x.x	x.x	x.x	x.x	x.x, x.x	0.xxx
	Placebo (N=X)		x	x.x	x.x	x.x	x.x	x.x, x.x	
Implementation note: Repeat for the Per Protocol Population.									

N = Number of subjects in the specified treatment group, duration of symptoms strata, and analysis population with positive GII test results at baseline.
n = Number of subjects with Norovirus GII results at Day 1 and Day 180.
Note: Adjustments based on Baseline Viral Titer.
P-value is the test of between-treatment differences for change in viral titer from Day 1 to Day 180.

Table with similar format:

Table 26: Change in Viral Titer between Day 1 and Day 180 by Treatment Group and Duration of Symptoms – Norovirus GI

Table 27: Change in Viral Titer between Day 1 and Day 180 by Treatment Group and Duration of Symptoms: Subgroup Sensitivity Analysis – Norovirus GII, mITT Population

[Implementation Note: If a transformation of the dependent variable is used, a footnote in the table will denote which transformation was used in the analyses. If the assumptions of ANCOVA cannot be met, only the observed mean, standard deviation and 95% confidence intervals of the unadjusted change in viral titer between Day 1 and Day 180 will be reported. If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable." If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses.]

Subgroup	Treatment Group	Duration of Symptoms	n	Observed Mean	Standard Deviation	Adjusted Mean	Standard Error	95% CI	P-value
Additional Nitazoxanide 500 mg[a]	Nitazoxanide 500 mg (N=X)	Acute (Baseline Mean = xx.x)	x	x.x	x.x	x.x	x.x	x.x, x.x	---
	Placebo (N=X)		x	x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N=X)	Chronic (Baseline Mean = xx.x)	x	x.x	x.x	x.x	x.x	x.x, x.x	---
	Placebo (N=X)		x	x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N=X)	Any Duration (Baseline Mean = xx.x)	x	x.x	x.x	x.x	x.x	x.x, x.x	0.xxx
	Placebo (N=X)		x	x.x	x.x	x.x	x.x	x.x, x.x	
Chromaturia[b]	Nitazoxanide 500 mg (N=X)	Acute (Baseline Mean = xx.x)	x	x.x	x.x	x.x	x.x	x.x, x.x	---
	Placebo (N=X)		x	x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N=X)	Chronic (Baseline Mean = xx.x)	x	x.x	x.x	x.x	x.x	x.x, x.x	---
	Placebo (N=X)		x	x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N=X)	Any Duration (Baseline Mean = xx.x)	x	x.x	x.x	x.x	x.x	x.x, x.x	0.xxx
	Placebo (N=X)		x	x.x	x.x	x.x	x.x	x.x, x.x	

N = Number of subjects in the specified treatment group, subgroup, and duration of symptoms strata with positive GII test results at baseline.
n = Number of subjects with Norovirus GII results at Day 1 and Day 180.
[a] Subjects that took additional Nitazoxanide 500 mg are excluded from the analyses.
[b] Subjects with unsolicited self-reported chromaturia (discoloration of urine) are excluded from the analyses.
Note: Adjustments based on Baseline Viral Titer Mean = xx.xx.
P-value is the test of between-treatment differences for change in viral titer from Day 1 to Day 180 for each subgroup.

Table with similar format:

Table 28: Change in Viral Titer between Day 1 and Day 180 by Treatment Group and Duration of Symptoms: Subgroup Sensitivity Analysis – Norovirus GI, mITT Population

Table 29: Exploratory Time to Event by Treatment Group and Duration of Symptoms – mITT Population

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable." If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses.

Event	Treatment Group	Duration of Symptoms	n	Median Time to Event		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
Clinical Improvement (Day 28)	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			
Clinical Improvement (Day 180)	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			
Repeat for Cessation of Vomiting, No Loss of Appetite, Cessation of Diarrhea, and 50% Reduction in Antimotility Agents								

N = Number of subjects in the specified treatment group, duration of symptoms strata, and analysis population.
n = Number of subjects with initial clinical resolution of symptoms.
Note: HR is the ratio of the hazard of the given event in each treatment group estimated from the Cox model. The ratio is Nitazoxanide 500 mg to Placebo.
HR for the 'Any Duration' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the likelihood ratio test.

Table 30: Exploratory Summary Statistics of Clinical Improvement Measures by Treatment Group – mITT Population

Clinical Improvement Measure	Statistic	Nitazoxanide 500 mg (N=X)	Placebo (N=X)
Days of Diarrhea (Day 28)	Mean	x.x	x.x
	Median	x.x	x.x
	Standard Deviation	x.x	x.x
	Minimum	X	x
	Maximum	X	x
	P-value[a]		0.xxx
Days of Diarrhea (Day 180)	Mean	x.x	x.x
	Median	x.x	x.x
	Standard Deviation	x.x	x.x
	Minimum	X	x
	Maximum	X	x
	P-value[a]		0.xxx
Implementation note: Repeat for Number of Type 6 or 7 stools and Days of IV Hydration/TPN Therapy			

N = Number of subjects in the specified treatment group and analysis population.
P-value is based on Wilcoxon-Mann-Whitney exact rank sum test.

Table 31: Patient-Reported Quality of Life by EuroQOL-5 Dimension and Study Day – Nitazoxanide 500 mg, mITT Population

EuroQOL-5 Dimension		Study Day					Total
		Day 1	Day 28	Day 60	Day 120	Day 180	
Mobility	No problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
	Problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
Self-Care	No problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
	Problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
Usual Activities	No problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
	Problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
Pain/Discomfort	No problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
	Problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
Anxiety/Depression	No problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)
	Problems	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)	n/N (x%)

Note: Number of questions answered as 'No Problems' (level 1) or 'Problems' (levels 2 or 3) for each EuroQOL-5 dimension at each given study day over the number of questions that were completed for the EuroQOL-5 dimension for the given study day.

Table with similar format:

Table 32: Patient-Reported Quality of Life by EuroQOL-5 Dimension and Study Day – Placebo, mITT Population

Table 33: Change in Patient-Reported Measures from Baseline to Day 28, 60, 120, and 180 by Treatment Group – mITT Population

[Implementation Note: If a transformation of the dependent variable is used, a footnote in the table will denote which transformation was used in the analyses for each patient-reported measure. If the assumptions of ANCOVA cannot be met, only the observed mean, standard deviation and 95% confidence intervals of the unadjusted change in patient reported measures will be reported.]

Patient-Reported Measure	Treatment Group	Study Day	Observed Mean	Standard Deviation	Adjusted Mean	Standard Error	95% CI	p-value
IBSQOL Quality of Life (Baseline QOL Mean = xx.xx)	Nitazoxanide 500 mg (N =X)	Day 28	x.x	x.x	x.x	x.x	x.x, x.x	---
	Placebo (N=X)		x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N =X)	Day 60	x.x	x.x	x.x	x.x	x.x, x.x	---
	Placebo (N=X)		x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N =X)	Day 120	x.x	x.x	x.x	x.x	x.x, x.x	---
	Placebo (N=X)		x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N =X)	Day 180	x.x	x.x	x.x	x.x	x.x, x.x	0.xxx
	Placebo (N=X)		x.x	x.x	x.x	x.x	x.x, x.x	
Implementation note: Repeat for Physical Function, Depression, Anxiety, Fatigue, GI Symptoms: Diarrhea, GI Symptoms: Nausea, GI Symptoms: Fecal Incontinence, GI Symptoms: Belly Pain.								

N = Number of subjects in the specified treatment group and analysis population with patient-reported measure on the given study day.
Note: Adjustments based on baseline mean values for each patient-reported measure.
P-value is the test of between-treatment differences for change in each patient-reported measure from baseline to Day 180.

Table 34: Time to Initial Clinical Resolution by Treatment Group and Co-Pathogen – mITT Population

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable. If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses."

Treatment Group	Co-Pathogens	n	Median Time to Initial Clinical Resolution		HR		P-value
			Estimate	95% CI	Estimate	95% CI	
Nitazoxanide 500 mg (N=X)	Present	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
Placebo (N=X)		x	x.x	x.x, x.x			
Nitazoxanide 500 mg (N=X)	Absent	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
Placebo (N=X)		x	x.x	x.x, x.x			
Nitazoxanide 500 mg (N=X)	Any Status	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
Placebo (N=X)		x	x.x	x.x, x.x			

N = Number of subjects in the specified treatment group, co-pathogen status strata, and analysis population.
n = Number of subjects with initial clinical resolution of symptoms.
Note: HR is the ratio of the hazard of initial clinical resolution in each treatment group estimated from the Cox model. The ratio is Nitazoxanide 500 mg to Placebo.
HR for the 'Any Status' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the likelihood ratio test.

Table 35: Time to First Negative Viral Load by Treatment Group and Co-Pathogen – Norovirus GII, mITT Population

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable." If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses.

Treatment Group	Co-Pathogens	n	Median Time to First Negative Viral Load		HR		P-value
			Estimate	95% CI	Estimate	95% CI	
Nitazoxanide 500 mg (N=X)	Present	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
Placebo (N=X)		x	x.x	x.x, x.x			
Nitazoxanide 500 mg (N=X)	Absent	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
Placebo (N=X)		x	x.x	x.x, x.x			
Nitazoxanide 500 mg (N=X)	Any Status	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
Placebo (N=X)		x	x.x	x.x, x.x			

N = Number of subjects in the specified treatment group, co-pathogen strata, and analysis population with positive GII test results at baseline.
n = Number of subjects with first negative GII viral load test result.
Note: HR is the ratio of the hazard of first negative GII viral load in each treatment group estimated from the Cox model. The ratio is Nitazoxanide 500 mg to Placebo.
HR for the 'Any Status' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the likelihood ratio test.

Table with similar format:

Table 36: Time to First Negative Viral Load by Treatment Group and Co-Pathogens – Norovirus GI, mITT Population

Table 37: Summary Statistics of Norovirus-Specific Serum and Stool IgA, IgM, and IgG Results by Study Day and Treatment Group – Immunogenicity Population

Assay	Study Day	Statistic	Nitazoxanide 500 mg (N=X)	Placebo (N=X)
NoV-Specific Serum IgA	**Day 1**	n	x	x
		GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
		Median	x.x	x.x
		Minimum	x	x
		Maximum	x	x
	Day 28	n	x	x
		GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
		Median	x.x	x.x
		Minimum	x	x
		Maximum	x	x
	Day 60	n	x	x
		GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
		Median	x.x	x.x
		Minimum	x	x
		Maximum	x	x
Implementation note: Repeat for NoV-Specific Serum IgG, Total Serum IgG, NoV-Specific/Total Serum IgG, NoV-Specific Serum IgM, NoV-Specific Stool IgA, NoV-Specific Stool IgG, and NoV-Specific Stool IgM.				

N = Number of subjects in the specified treatment group and analysis population.
n = Number of subjects with valid results at the given timepoint for the given assay.

Table 38: Norovirus-Specific Serum and Stool IgA, IgM, and IgG Results by Study Day and Treatment Group – Immunogenicity Population

Assay	Study Day	Statistic	Nitazoxanide 500 mg (N=X)	Placebo (N=X)
NoV-Specific Serum IgA	**Day 28**	n	x	x
		GMFR (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
		Proportion Seroresponders (95% CI)[a]	x.x (x.x, x.x)	x.x (x.x, x.x)
	Day 60	n	x	x
		GMFR (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
		Proportion Seroresponders (95% CI)[a]	x.x (x.x, x.x)	x.x (x.x, x.x)
Implementation note: Repeat for NoV-Specific Serum IgG, Total Serum IgG, NoV-Specific/Total Serum IgG, NoV-Specific Serum IgM, NoV-Specific Stool IgA, NoV-Specific Stool IgG, and NoV-Specific Stool IgM.				

N = Number of subjects in the specified treatment group and analysis population.
n = Number of subjects with valid results at the given timepoint for the given assay.
[a]95% CIs are Wilson score two-sided confidence intervals.

Table 39: Change in Norovirus-Specific Immunoglobulin Assays between Day 1 and Study Day 28 and 60 by Treatment Group – Immunogenicity Population

[Implementation Note: If a transformation of the dependent variable is used, a footnote in the table will denote which transformation was used in the analyses. If the assumptions of ANCOVA cannot be met, only the observed mean, standard deviation and 95% confidence intervals of the unadjusted change in assays between Day 1 and Day 28 and Day 1 and Day 60 will be reported.]

Norovirus-Specific Assay	Treatment Group	Study Day	Observed Mean	Standard Deviation	Adjusted Mean	Standard Error	95% CI	P-value
Serum IgA (Baseline Serum IgA Mean = xx.xx)	Nitazoxanide 500 mg (N=X)	Day 28	x.x	x.x	x.x	x.x	x.x, x.x	0.xxx
	Placebo (N=X)		x.x	x.x	x.x	x.x	x.x, x.x	
	Nitazoxanide 500 mg (N=X)	Day 60	x.x	x.x	x.x	x.x	x.x, x.x	0.xxx
	Placebo (N=X)		x.x	x.x	x.x	x.x	x.x, x.x	
Implementation note: Repeat for Serum IgG, Serum IgM, Stool IgA, Stool IgG, and Stool IgM.								

N = Number of subjects in the specified treatment group and analysis population.
Note: Adjustments based on baseline mean values for each assay type.
P-value is the test of between-treatment differences for change in each assay type from Day 1 to the given study day.

Table 40: Mixed Effects Model Coefficient Estimates – Norovirus-Specific Serum IgA, Immunogenicity Population

[Implementation Note: If a transformation is used, a footnote in the table will denote which transformation was used in the analyses. If the relationship between Norovirus-specific serum IgA and time is linear, the coefficients listed in the table will only include β0 - β3 and the descriptions of the coefficients will be "Intercept", "Slope", "Intercept * Treatment", and "Slope * Treatment", respectively.]

Coefficient	Estimate	Standard Error	P-value
β_0: Intercept			
β_1: Treatment			
β_2: Day 28			
β_3: Day 28 * Treatment			
β_4: Day 60			
β_5: Day 60 * Treatment			

Tables with similar format:

Table 41: Mixed Effects Model Coefficient Estimates – Norovirus-Specific Stool IgA, Immunogenicity Population

Table 42: Mixed Effects Model Coefficient Estimates – Norovirus-Specific Serum IgG, Immunogenicity Population

Table 43: Mixed Effects Model Coefficient Estimates – Norovirus-Specific Stool IgG, Immunogenicity Population

Table 44: Mixed Effects Model Coefficient Estimates – Norovirus-Specific Serum IgM, Immunogenicity Population

Table 45: Mixed Effects Model Coefficient Estimates – Norovirus-Specific Stool IgM, Immunogenicity Population

Table 46: Correlation of Change in T-Cell Subset from Day 1 to Day 180 vs Clinical Resolution of Symptoms and Negative PCR by Treatment Group – Immunogenicity Population

T-Cell Subset	First Day of Clinical Resolution			First Day with Negative PCR		
	Pearson Correlation (95% CI)		P-value	Pearson Correlation (95% CI)		P-value
	Nitazoxanide 500 mg	Placebo		Nitazoxanide 500 mg	Placebo	
Total Lymphocyte Count	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
CD3 + Cells	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
CD3+ Cells/Lymphocytes	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
CD4+ Cells	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
CD4+ Cells/Lymphocytes	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
CD8+ Cells	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
CD8+ Cells/Lymphocytes	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx

Table 47: Correlation of Change in Norovirus-Specific Immunoglobulin Assays vs Clinical Resolution of Symptoms and Negative PCR by Study Day and Treatment Group – Immunogenicity Population

	First Day of Clinical Resolution			First Day with Negative PCR		
	Pearson Correlation (95% CI)		P-value	Pearson Correlation (95% CI)		P-value
Norovirus-Specific Assay	Nitazoxanide 500 mg	Placebo		Nitazoxanide 500 mg	Placebo	
Serum IgA (Day 28)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
Serum IgA (Day 60)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
Stool IgA (Day 28)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
Stool IgA (Day 60)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	0.xxx
Implementation note: Repeat for Serum IgG (Day 28), Serum IgG (Day 60), Stool IgG (Day 28), Stool IgG (Day 60), Serum IgM (Day 28), Serum IgM (Day 60), Stool IgM (Day 28), and Stool IgM (Day 60).						

Note: Change in Norovirus-specific assay is the change Day 1 to the given study day (Day 28 or Day 60).

Table 48: Time to Initial Clinical Resolution by Test, Treatment Group and Secretor Status – mITT Population

Implementation Note: If an estimate is not calculable, insert "NC" in the cell and add a footnote "NC = Not calculable." If a subgroup has less than 5 subjects per treatment group, then remove rows and add footnote specifying which group(s) are excluded from analyses.

Test	Treatment Group	Secretor Status	n	Median Time to Initial Clinical Resolution		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
Genotype	Nitazoxanide 500 mg (N=X)	Secretor	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Non-Secretor	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Status	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			
Phenotype	Nitazoxanide 500 mg (N=X)	Secretor	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Non-Secretor	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Status	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			

N = Number of subjects in the specified treatment group and secretor status strata with valid results for the given test type.
n = Number of subjects with initial clinical resolution of symptoms.
Note: HR is the ratio of the hazard of initial clinical resolution in each treatment group estimated from the Cox model. The ratio is Nitazoxanide 500 mg to Placebo.
HR for the 'Any Status' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the likelihood ratio test.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 49: Overall Summary of Adverse Events

	Nitazoxanide 500 mg (N = X)		Placebo (N = X)		All Subjects (N = X)	
Subjects[a] with	n	%	n	%	n	%
At least one unsolicited adverse event	x	x	x	x	x	x
At least one unsolicited non-serious adverse event through 60 days	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x
Not yet assessed						
At least one severe (Grade 3) unsolicited adverse event	x	x	x	x	x	x
Related	x	x	x	x	x	x
Unrelated	x	x	x	x	x	x
At least one serious adverse event[b]	x	x	x	x	x	x
At least one serious adverse event through 60 days[b]	x	x	x	x	x	x
At least one related, serious adverse event	x	x	x	x	x	x
At least one adverse event leading to early termination[c]	x	x	x	x	x	x
At least one laboratory adverse event[d] through 60 days	x	x	x	x	x	x
At least one hospitalization	x	x	x	x	x	x
At least one hospitalization through 60 days	x	x	x	x	x	x

N = Number of subjects in the Safety Population
[a] Subjects are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Section 14.3.2.
[c] As reported on the Adverse Event eCRF.
[d] Laboratory adverse events include WBC, Hemoglobin, Platelet count, Creatinine, Alkaline Phosphatase, ALT, AST, BUN, and Bilirubin.

Table 50: Subject-Level Rates of Adverse Events through Day 60 and Differences between Treatment Groups – Safety Population

	Nitazoxanide 500 mg (N=X)		Placebo (N = X)		Difference[b]		p-value[c]
Subjects[a] with at least one:	**n**	**%**	**n**	**%**	**Estimate**	**95% CI**	
Unsolicited Non-Serious Adverse Event	x	x	x	x	x.xx	(x.xx,x.xx)	0.xxxx
Laboratory Adverse Event[d]							
Serious Adverse Event							
Hospitalization							

N = Number of subjects in the Safety Population.
[a] Subjects are counted once for each category regardless of the number of events.
[b] Difference is the difference in proportions of subjects with at least one adverse event in the specified category between Nitazoxanide 500 mg and Placebo.
[c] P-value is based on Barnard's exact test at the 5% two-sided level of significance.
[d] Laboratory adverse events include WBC, Hemoglobin, Platelet count, Creatinine, Alkaline Phosphatase, ALT, AST, BUN, and Bilirubin.

Table 51: Subject-Level Rates of Adverse Events through Day 60 and Differences between Treatment Groups: Chromaturia Sensitivity Analysis – Safety Population

	Nitazoxanide 500 mg (N=X)		Placebo (N = X)		Difference[b]		p-value[c]
Subjects[a] with at least one:	**n**	**%**	**n**	**%**	**Estimate**	**95% CI**	
Unsolicited Non-Serious Adverse Event	x	x	x	x	x.xx	(x.xx,x.xx)	0.xxxx
Laboratory Adverse Event[d]							
Serious Adverse Event							
Hospitalization							

N = Number of subjects in the Safety Population who do not report chromaturia.
[a] Subjects are counted once for each category regardless of the number of events.
[b] Difference is the difference in proportions of subjects with at least one adverse event in the specified category between Nitazoxanide 500 mg and Placebo.
[c] P-value is based on Barnard's exact test at the 5% two-sided level of significance.
[d] Laboratory adverse events include WBC, Hemoglobin, Platelet count, Creatinine, Alkaline Phosphatase, ALT, AST, BUN, and Bilirubin.

Table 52: Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA Preferred Term, System Organ Class, and Treatment Group – Safety Population

MedDRA Preferred Term	MedDRA System Organ Class	Nitazoxanide 500 mg (N=X)			Placebo (N=X)			All Subjects (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc.	Etc.									
Other (Non-serious) Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc	Etc									

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

Table 53: Summary of Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and Study Phase – Nitazoxanide 500 mg, Safety Population

MedDRA System Organ Class	MedDRA Preferred Term	Day 1 - 28 Treatment Phase (N=X)				Day 29 - 60 Longitudinal Phase (N=X)				Any Time (N=X)			
		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
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

N = Number of subjects in the Safety Population.
n = number of subjects reporting event. A subject is only counted once per PT/time point.
Events = total frequency of events reported.
Note: 95% CIs are Wilson score two-sided confidence intervals.

Tables with similar format:

Table 54: Summary of Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and Study Phase – Placebo, Safety Population

Table 55: Summary of Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, and Study Phase – All Subjects, Safety Population

Table 56: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group – Nitazoxanide 500 mg, Safety Population, N=x

MedDRA System Organ Class	MedDRA Preferred Term	Any Incidence		Severity						Relationship to Treatment			
				Mild		Moderate		Severe		Related		Not Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	PT 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	PT 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the Safety Population.
n = number of subjects reporting event. A subject is only counted once per PT/time point.

Tables with similar format:

Table 57: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group – Placebo, Safety Population, N=x

Table 58: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group – All Subjects, Safety Population, N=x

Table 59: Related Unsolicited Adverse Events During Treatment Phase (Days 1 – 28) by MedDRA System Organ Class, Preferred Term, and Treatment Group – Safety Population

MedDRA System Organ Class	MedDRA Preferred Term	Nitazoxanide 500 mg (N = X)			Placebo (N = X)			All Subjects (N = X)		
		n	%	Events	n	%	Events	n	%	Events
Any SOC	Any PT	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any PT									
	[PT 1]									
	[PT 2]									
[SOC 2]	Any PT	x	xx	x	x	xx	x	x	xx	x
	[PT 1]									
	[PT 2]									

N = Number of subjects in the Safety Population.
n = number of subjects reporting event. A subject is only counted once per PT/time point.
Events = total frequency of events reported.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 60: Listing of Serious Adverse Events

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR. 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'. Add columns for MedDRA HLT or LLT depending on halting criteria or other study needs. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Subject ID, Associated with Dose No., and No. of Days Post Associated Dose.]

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

Table 61: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

[Implementation Note: This listing is included in the tables document, as it is included in the body of the CSR. 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'. Add columns for MedDRA HLT or LLT depending on halting criteria or other study needs. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Subject ID, Associated with Dose No., and No. of Days Post Associated Dose. If the event is related, show N/A in the Alternative Etiology column and add a footnote defining N/A = Not applicable.]

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

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

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

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 62: Listing of Abnormal Laboratory Results - Chemistry

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

Table 63: Listing of Abnormal Laboratory Results - Hematology

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

14.3.4 Displays of Laboratory Results

14.3.4.1 Chemistry Results

Table 64: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Chemistry Parameter

[Implementation Note: Generate one table for "Any Chemistry Parameter" and one table for each chemistry parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity.]

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	Nitazoxanide 500 mg	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 7	Nitazoxanide 500 mg											
	Placebo											
Day 28	Nitazoxanide 500 mg											
	Placebo											
Day 180	Nitazoxanide 500 mg											
	Placebo											
Max Severity Post Baseline	Nitazoxanide 500 mg											
	Placebo											

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

Table 65: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Creatinine

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Nitazoxanide 500 mg	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 7	Nitazoxanide 500 mg											
	Placebo											
Day 28	Nitazoxanide 500 mg											
	Placebo											
Day 180	Nitazoxanide 500 mg											
	Placebo											
Max Severity Post Baseline	Nitazoxanide 500 mg											
	Placebo											

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

Tables with similar format:

Table 66: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – BUN

Table 67: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Alkaline Phosphatase

Table 68: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – AST

Table 69: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – ALT

Table 70: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Total Bilirubin

Table 71: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Chemistry Parameter

[Implementation Note: Generate one table for "Any Chemistry Parameter" and one table for each chemistry parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity.]

Any Chemistry Parameter Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
Baseline	Nitazoxanide 500 mg	x	x	xx	x	xx	x	xx	x	xx
	Placebo									
Day 7	Nitazoxanide 500 mg									
	Placebo									
Day 28	Nitazoxanide 500 mg									
	Placebo									
Day 180	Nitazoxanide 500 mg									
	Placebo									
Max Severity Post Baseline	Nitazoxanide 500 mg									
	Placebo									

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

Table 72: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Creatinine

[Implementation Note: Generate one table for "Any Chemistry Parameter" and one table for each chemistry parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
Baseline	Nitazoxanide 500 mg	x	x	xx	x	xx	x	xx	x	xx
	Placebo									
Day 7	Nitazoxanide 500 mg									
	Placebo									
Day 28	Nitazoxanide 500 mg									
	Placebo									
Day 180	Nitazoxanide 500 mg									
	Placebo									
Max Severity Post Baseline	Nitazoxanide 500 mg									
	Placebo									

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

Tables with similar format:

Table 73: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – BUN

Table 74: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Alkaline Phosphatase

Table 75: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – AST

Table 76: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – ALT

Table 77: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Total Bilirubin

Table 78: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Creatinine (mg/dL)

[Implementation Note: Generate one table for each chemistry parameter. For calculated fields (Mean, SD, Median), decimal place should be the format in which the data were collected + 1 extra place. For Min, Max, decimal place should be in the same format in which the data were collected.]

[Repeat for each Chemistry Laboratory Parameter, number each table separately]

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Nitazoxanide 500 mg	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Placebo					
Day 7	Nitazoxanide 500 mg					
	Placebo					
Day 7, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 28	Nitazoxanide 500 mg					
	Placebo					
Day 28, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 180	Nitazoxanide 500 mg					
	Placebo					
Day 180, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					

N = Number of subjects in the Safety Population with reported results at the specified time point.

Tables with similar format:

Table 79: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – BUN (mg/dL)

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

Table 81: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – AST (U/L)

Table 82: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – ALT (U/L)

Table 83: Laboratory Summary Statistics by Parameter Time Point, and Treatment Group – Total Bilirubin (mg/dL)

14.3.4.2 Hematology Results

Table 84: Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Hematology Parameter

[Implementation Note: Generate one table for "Any Hematology Parameter" and one table for each hematology parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity.]

Any Hematology Parameter Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Nitazoxanide 500 mg	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 7	Nitazoxanide 500 mg											
	Placebo											
Day 28	Nitazoxanide 500 mg											
	Placebo											
Day 180	Nitazoxanide 500 mg											
	Placebo											
Max Severity Post Baseline	Nitazoxanide 500 mg											
	Placebo											

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

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

Time Point	Treatment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Nitazoxanide 500 mg	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo																	
Day 7	Nitazoxanide 500 mg																	
	Placebo																	
Day 28	Nitazoxanide 500 mg																	
	Placebo																	
Day 180	Nitazoxanide 500 mg																	
	Placebo																	
Max Severity Post Baseline	Nitazoxanide 500 mg																	
	Placebo																	

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

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

[Implementation Note: Generate one table for "Any Hematology Parameter" and one table for each hematology parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Nitazoxanide 500 mg	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
Day 7	Nitazoxanide 500 mg											
	Placebo											
Day 28	Nitazoxanide 500 mg											
	Placebo											
Day 180	Nitazoxanide 500 mg											
	Placebo											
Max Severity Post Baseline	Nitazoxanide 500 mg											
	Placebo											

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

Table with similar format:

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

Table 88: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Any Hematology Parameter

[Implementation Note: Generate one table for "Any Chemistry Parameter" and one table for each chemistry parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity.]

Any Hematology Parameter Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
Baseline	Nitazoxanide 500 mg	x	x	xx	x	xx	x	xx	x	xx
	Placebo									
Day 7	Nitazoxanide 500 mg									
	Placebo									
Day 28	Nitazoxanide 500 mg									
	Placebo									
Day 180	Nitazoxanide 500 mg									
	Placebo									
Max Severity Post Baseline	Nitazoxanide 500 mg									
	Placebo									

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

Table 89: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – WBC

Time Point	Treatment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Nitazoxanide 500 mg	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo															
Day 7	Nitazoxanide 500 mg															
	Placebo															
Day 28	Nitazoxanide 500 mg															
	Placebo															
Day 180	Nitazoxanide 500 mg															
	Placebo															
Max Severity Post Baseline	Nitazoxanide 500 mg															
	Placebo															

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

Table 90: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Hemoglobin

[Implementation Note: Generate one table for "Any Chemistry Parameter" and one table for each chemistry parameter. If a parameter has a grading scale that includes grading for both high and low, then include one column for each severity for high and low, as shown in the second sample table below. If not, then just include one column per severity, as shown in the first sample table. The "Any Parameter" table will just summarize one column per severity.]

Time Point	Treatment Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%	n	%
Baseline	Nitazoxanide	x	x	xx	x	xx	x	xx	x	xx
	Placebo									
Day 7	Nitazoxanide									
	Placebo									
Day 28	Nitazoxanide									
	Placebo									
Day 180	Nitazoxanide									
	Placebo									
Max Severity Post Baseline	Nitazoxanide									
	Placebo									

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

Table with similar format:

Table 91: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Time Point, and Treatment Group – Platelets

Table 92: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – WBC (10^9/L)

[Implementation Note: Generate one table for each hematology parameter. For calculated fields (Mean, SD, Median), decimal place should be the format in which the data were collected + 1 extra place. For Min, Max, decimal place should be in the same format in which the data were collected.]

[Repeat for each Hematology Laboratory Parameter and a table for each Parameter's Change from Baseline, number each table separately]

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Nitazoxanide 500 mg	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Placebo					
Day 7	Nitazoxanide 500 mg					
	Placebo					
Day 7, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 28	Nitazoxanide 500 mg					
	Placebo					
Day 28, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 180	Nitazoxanide 500 mg					
	Placebo					
Day 180, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					

N = Number of subjects in the Safety Population with reported results at the specified time point.

Table with similar format:

Table 93: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hemoglobin (g/dL)

Table 94: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Platelets (10^9/L)

Table 95: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Monocytes (10^9/L)

Table 96: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hematocrit (%)

Table 97: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Mean Corpuscular Volume (fL)

Table 98: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Neutrophils (10^9/L)

Section 14.3.4.4 Displays of Hospitalizations, Allograft Rejection, Graft Loss, Death

Table 107: Duration of Hospitalization (Days) Summary Statistics by Treatment Group and Study Day – Safety Population

Study Day	Statistic	Nitazoxanide 500 mg (N=X)	Placebo (N=X)
Day 28	n	x	x
	Mean	x.x	x.x
	Median	x.x	x.x
	Standard Deviation	x.x	x.x
	Minimum	x	x
	Maximum	x	x
	P-value[a]		0.xxx
Day 180	N	x	x
	Mean	x.x	x.x
	Median	x.x	x.x
	Standard Deviation	x.x	x.x
	Minimum	x	x
	Maximum	x	x
	P-value[a]		0.xxx

N = Number of subjects in the specified treatment group and analysis population.
n = Number of subjects in each treatment group who were hospitalized by the given timepoint.
[a] P-value is based on Wilcoxon Mann-Whitney exact rank sum test.

Table 108: Natural History of Disease Time to Event by Treatment Group and Duration of Symptoms – mITT Population

Event	Treatment Group	Duration of Symptoms	n	Median Time to Event		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
Allograft Rejection	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			
Graft Loss	Nitazoxanide 500 mg (N=X)	Acute	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Chronic	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo (N=X)		x	x.x	x.x, x.x			
	Nitazoxanide 500 mg (N=X)	Any Duration	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo (N=X)		x	x.x	x.x, x.x			
Implementation note: Repeat for Death and Withdrawal from Study.								

N = Number of subjects in the specified treatment group, duration of symptoms strata, and analysis population.
n = Number of subjects with initial clinical resolution of symptoms.
Note: HR is the ratio of the hazard of the given event in each treatment group estimated from the Cox model. The ratio is Nitazoxanide 500 mg to Placebo.
HR for the 'Any Duration' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the likelihood ratio test.

14.3.5 Displays of Vital Signs

Table 109: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Temperature (°F)

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Nitazoxanide 500 mg	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Placebo					
Day 7	Nitazoxanide 500 mg					
	Placebo					
Day 7, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 14	Nitazoxanide 500 mg					
	Placebo					
Day 14, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 21	Nitazoxanide 500 mg					
	Placebo					
Day 21, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 28	Nitazoxanide 500 mg					
	Placebo					
Day 28, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 60	Nitazoxanide 500 mg					
	Placebo					
Day 60, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 120	Nitazoxanide 500 mg					
	Placebo					

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Day 120, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					
Day 180	Nitazoxanide 500 mg					
	Placebo					
Day 180, Change from Baseline	Nitazoxanide 500 mg					
	Placebo					

N = Number of subjects in the Safety Population with reported results at the specified time point.

Table with similar format:

Table 110: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Weight (kg)

Table 111: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Systolic Blood Pressure (mmHg)

Table 112: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Diastolic Blood Pressure (mmHg)

Table 113: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Respiration (breaths/minute)

Table 114: Vital Signs Summary Statistics by Parameter, Time Point, and Treatment Group – Pulse (beats/minute)

14.4 Summary of Concomitant Medications

Table 115: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

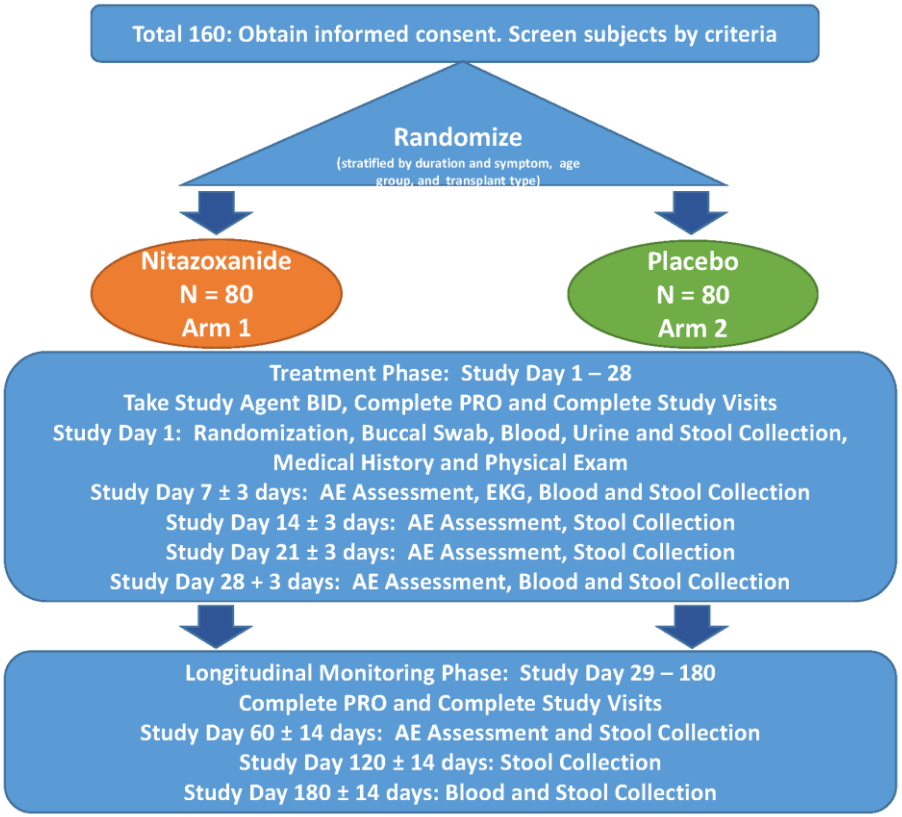
WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Nitazoxanide 500 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
[ATC Level 1 – 2]	Any [ATC 1 – 2						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						

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

APPENDIX 2. FIGURE MOCK-UPS

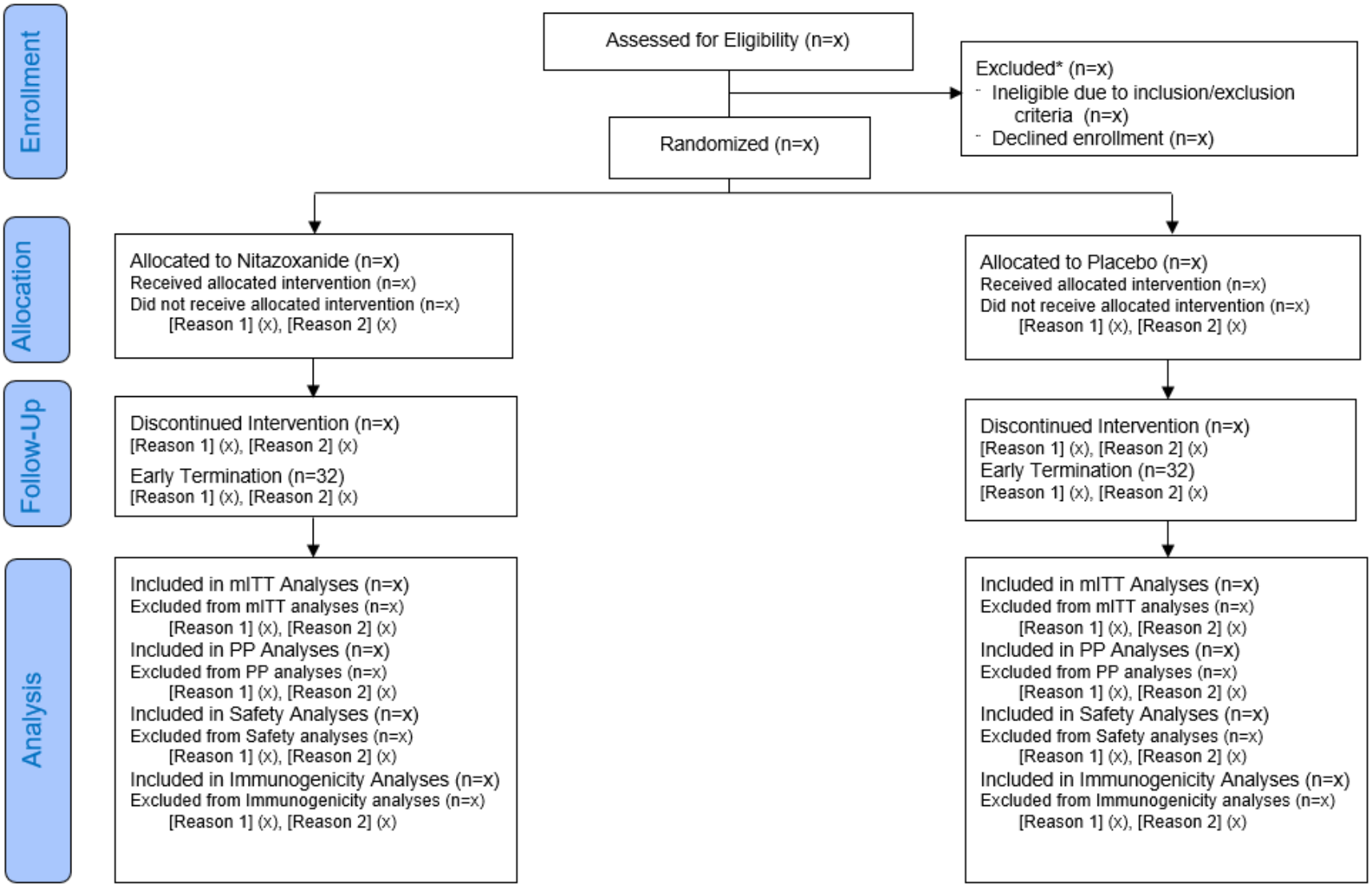
LIST OF FIGURES

Figure 1: Study Design



10.1 Disposition of Subjects

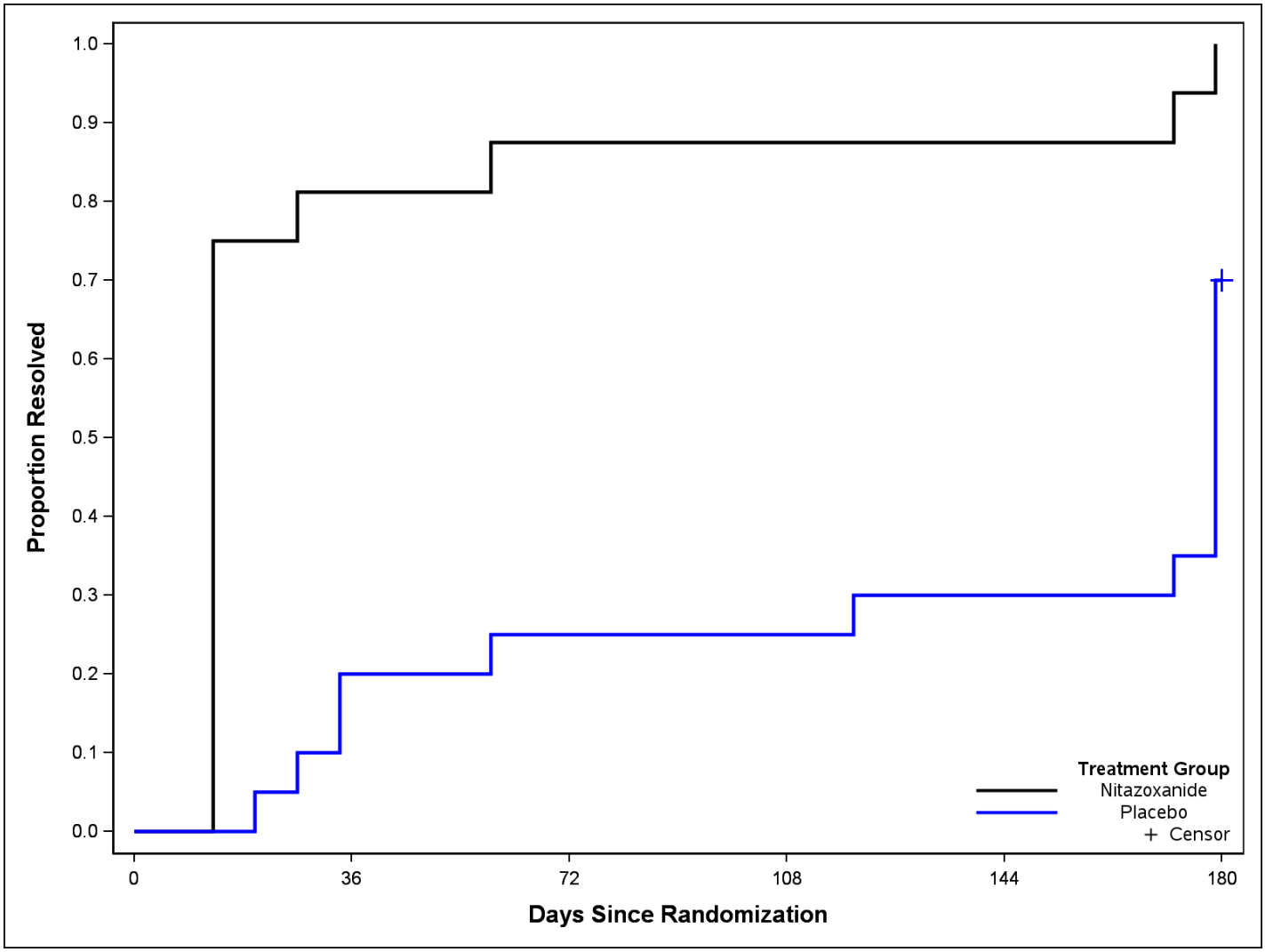
Figure 2: CONSORT Flow Diagram



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

Figure 3: Kaplan-Meier Curves of Time to Initial Clinical Resolution by Treatment Group – mITT Population

[Implementation Note: Include (N=X) for each group in legend.]



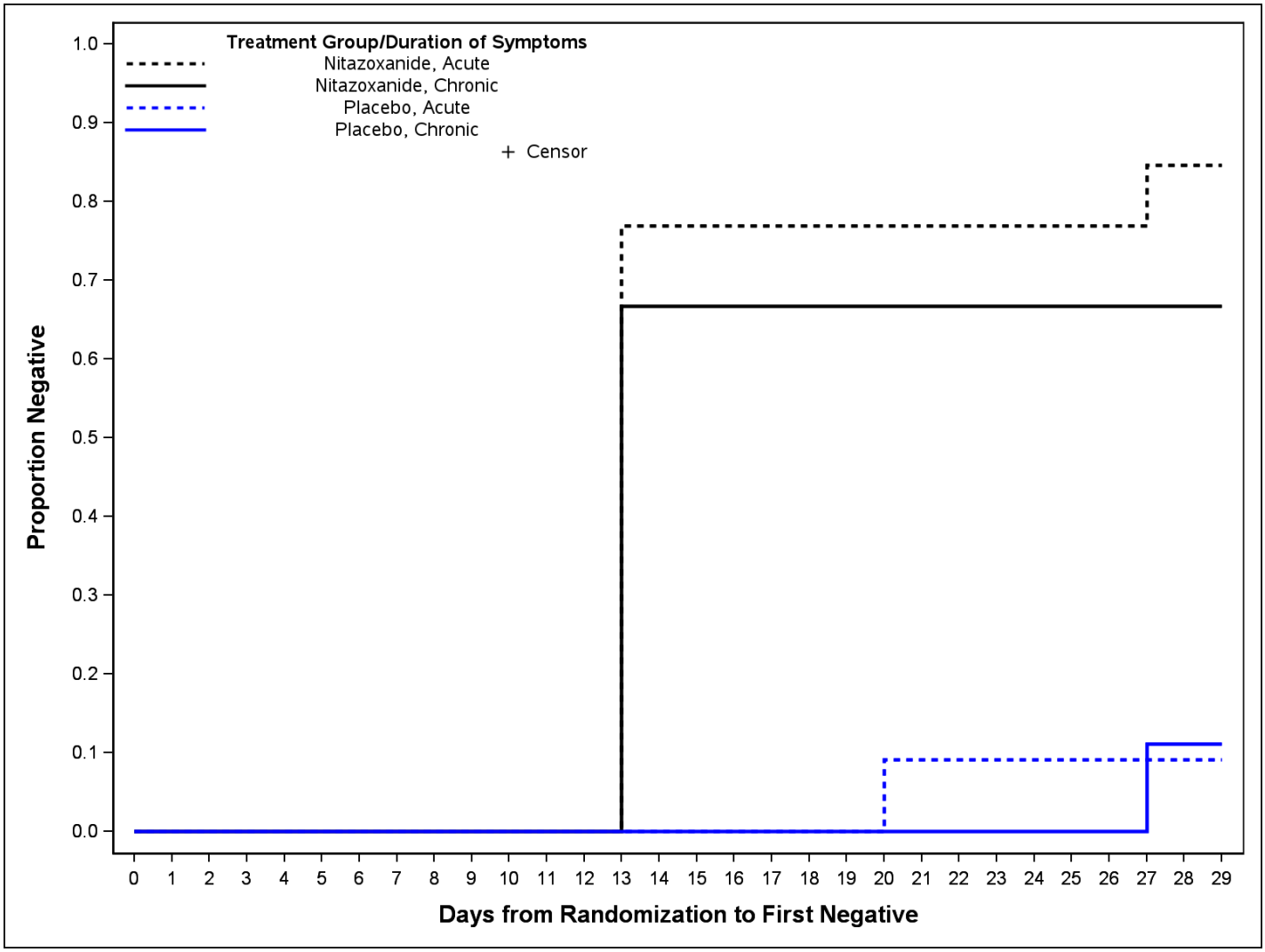
Figures with similar format:

Figure 4: Kaplan-Meier Curves of Time to Initial Clinical Resolution by Treatment Group – Per Protocol Population

Figure 5: Kaplan-Meier Curves of Time to Initial Clinical Resolution by Treatment Group: Worst Case Scenario Sensitivity Analysis – mITT Population

Figure 6: Kaplan-Meier Curves of Time to Initial Clinical Resolution by Treatment Group and Duration of Symptoms – mITT Population

[Implementation Note: Y axis will be "Proportion Resolved", x axis will be "Days Since Randomization". Curves will include all subjects in the mITT Population that tested positive for GII at baseline. Include (N=X) for each group in legend. If subgroup has less than 5 subjects per treatment group, add footnote describing exclusion from figure.]



Figures with similar format:

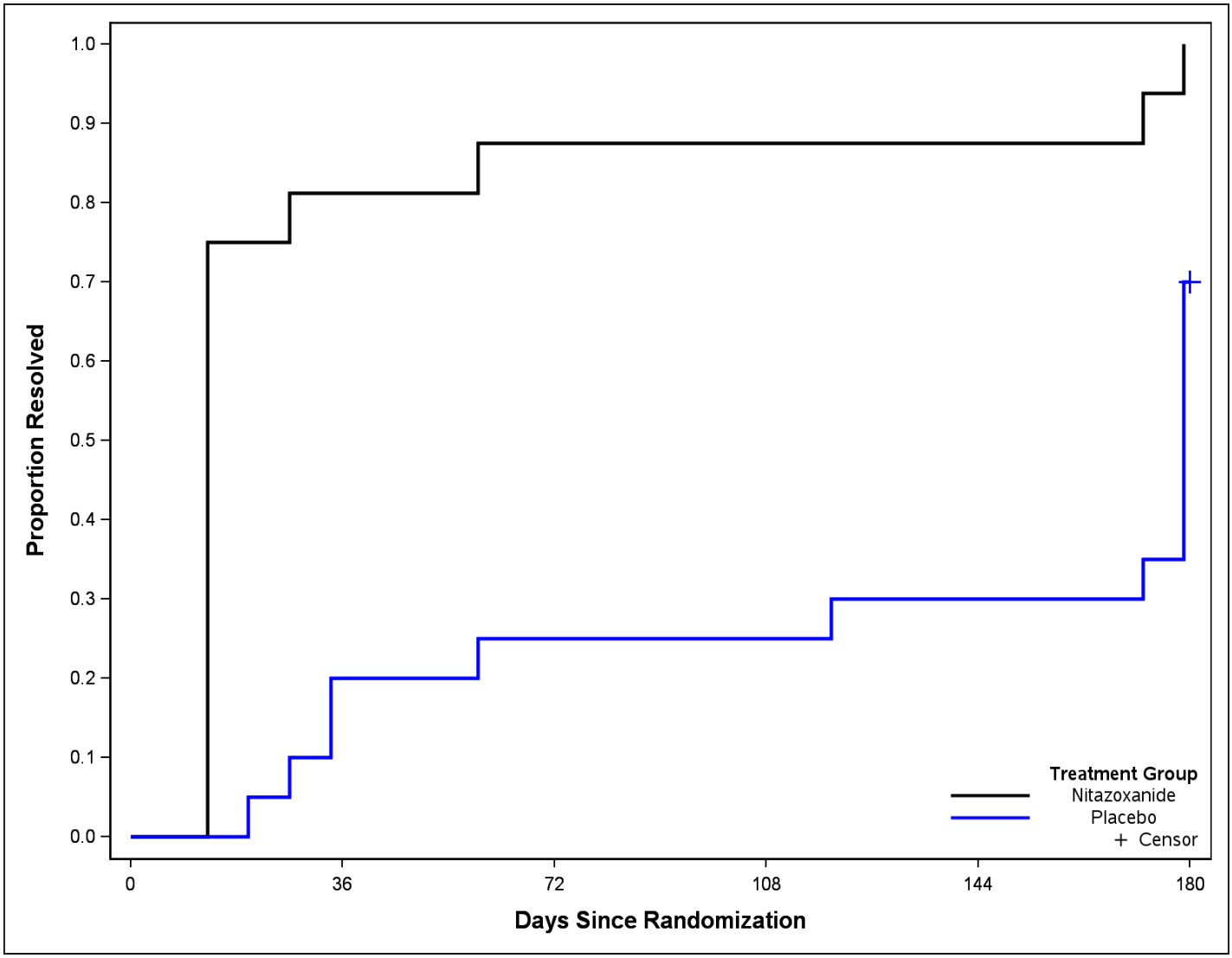
Figure 7: Kaplan-Meier Curves of Time to Initial Clinical Resolution by Treatment Group and Duration of Symptoms – Per Protocol Population

Figure 8: Kaplan-Meier Curves of Time to Initial Clinical Resolution by Treatment Group and Duration of Symptoms: Worst Case Scenario Sensitivity Analysis – mITT Population

Figure 9: Kaplan-Meier Curves of Time to Initial Clinical Resolution by Treatment Group and Diary Compliance – mITT Population

Figure 10: Kaplan-Meier Curves of Time to First Negative Viral Load by Treatment Group – Norovirus GII, mITT Population

[Implementation Note: Y axis will be "Proportion Negative", x axis will be "Days Since Randomization". Curves will include all subjects in the mITT Population that tested positive for GII at baseline. Include (N=X) for each group in legend.]



Tables with similar format:

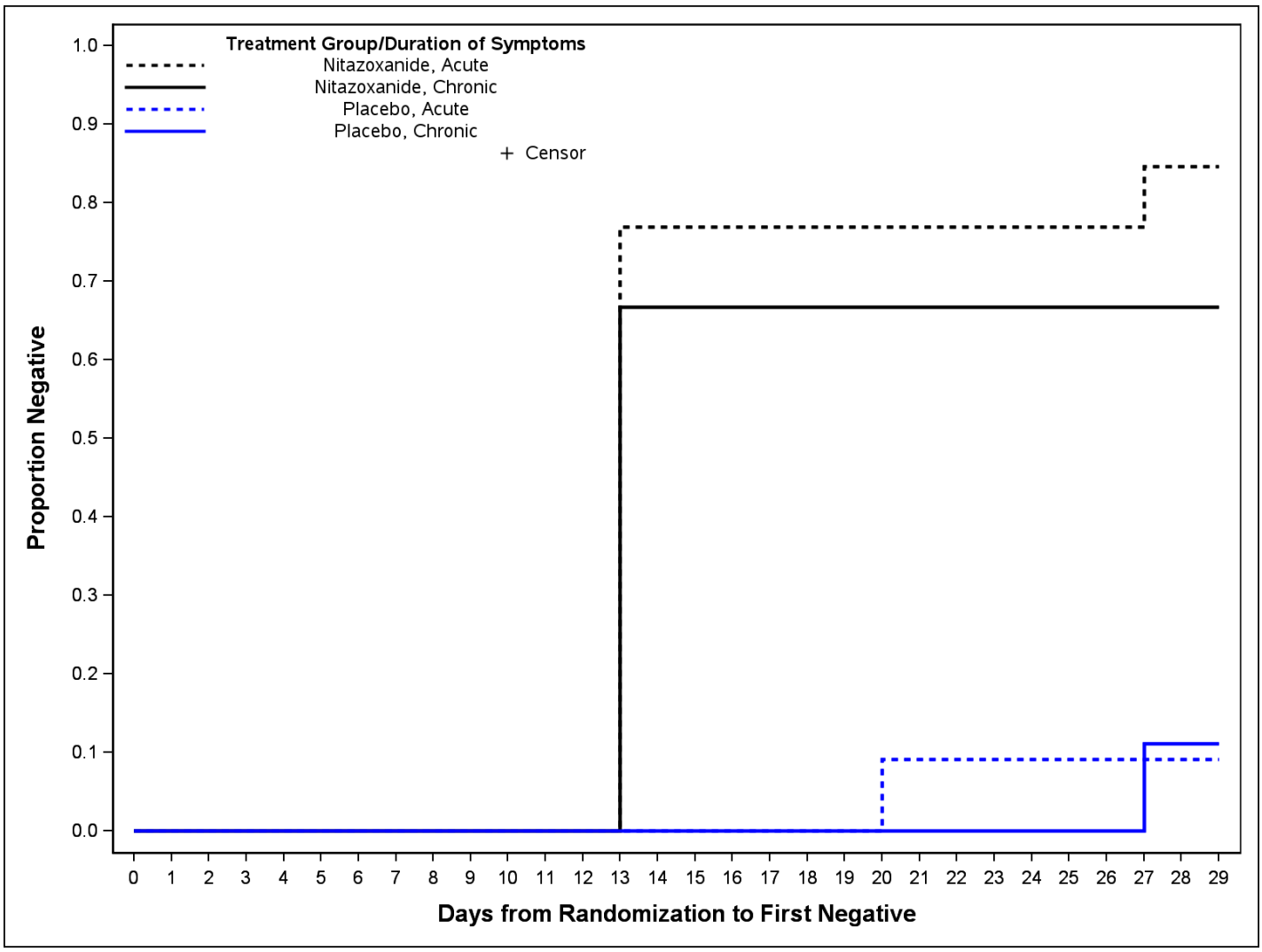
Figure 11: Kaplan-Meier Curves of Time to First Negative Viral Load by Treatment Group – Norovirus GII, Per Protocol Population

Figure 12: Kaplan-Meier Curves of Time to First Negative Viral Load by Treatment Group – Norovirus GI, mITT Population

Figure 13: Kaplan-Meier Curves of Time to First Negative Viral Load by Treatment Group – Norovirus GI, Per Protocol Population

Figure 14: Kaplan-Meier Curves of Time to First Negative Viral Load by Treatment Group and Duration of Symptoms – Norovirus GII, mITT Population

[Implementation Note: Y axis will be "Proportion Negative", x axis will be "Days Since Randomization". Curves will include all subjects in the mITT Population that tested positive for GII at baseline. Include (N=X) for each group in legend. If subgroup has less than 5 subjects per treatment group, add footnote describing exclusion from figure.]



Figures with similar format:

Figure 15: Kaplan-Meier Curves of Time to First Negative Viral Load by Treatment Group and Duration of Symptoms – Norovirus GI, mITT Population

Figure 16: Forest Plot of Change in Viral Titer between Day 1 and Day 180 by Treatment Group and Duration of Symptoms – Norovirus GII, mITT Population

[Implementation Note: Include (N=X) for each group in y axis. If subgroup has less than 5 subjects per treatment group, add footnote describing exclusion from figure. X axis title is "Adjusted Mean and 95% CI".]

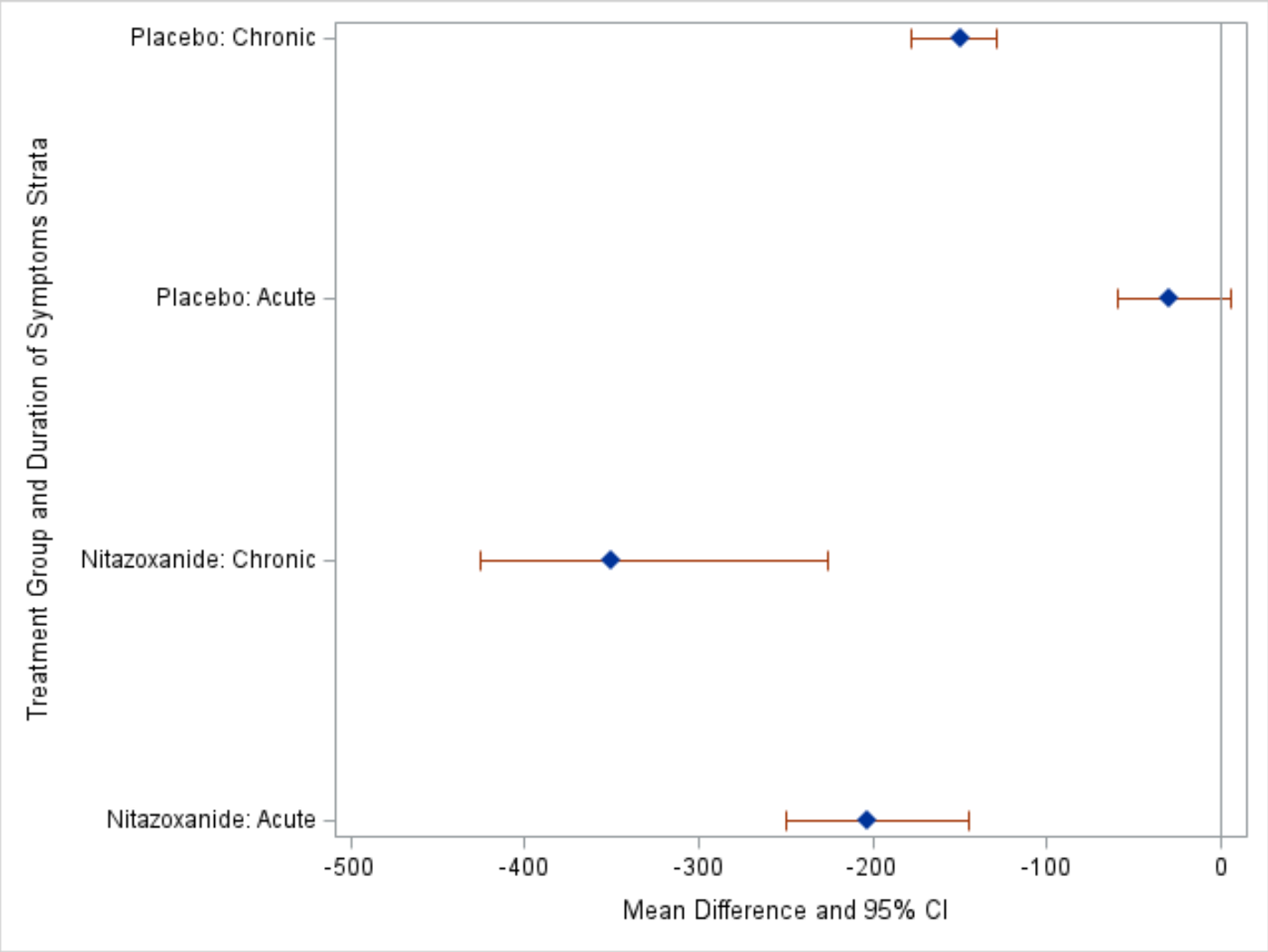


Figure with similar format:

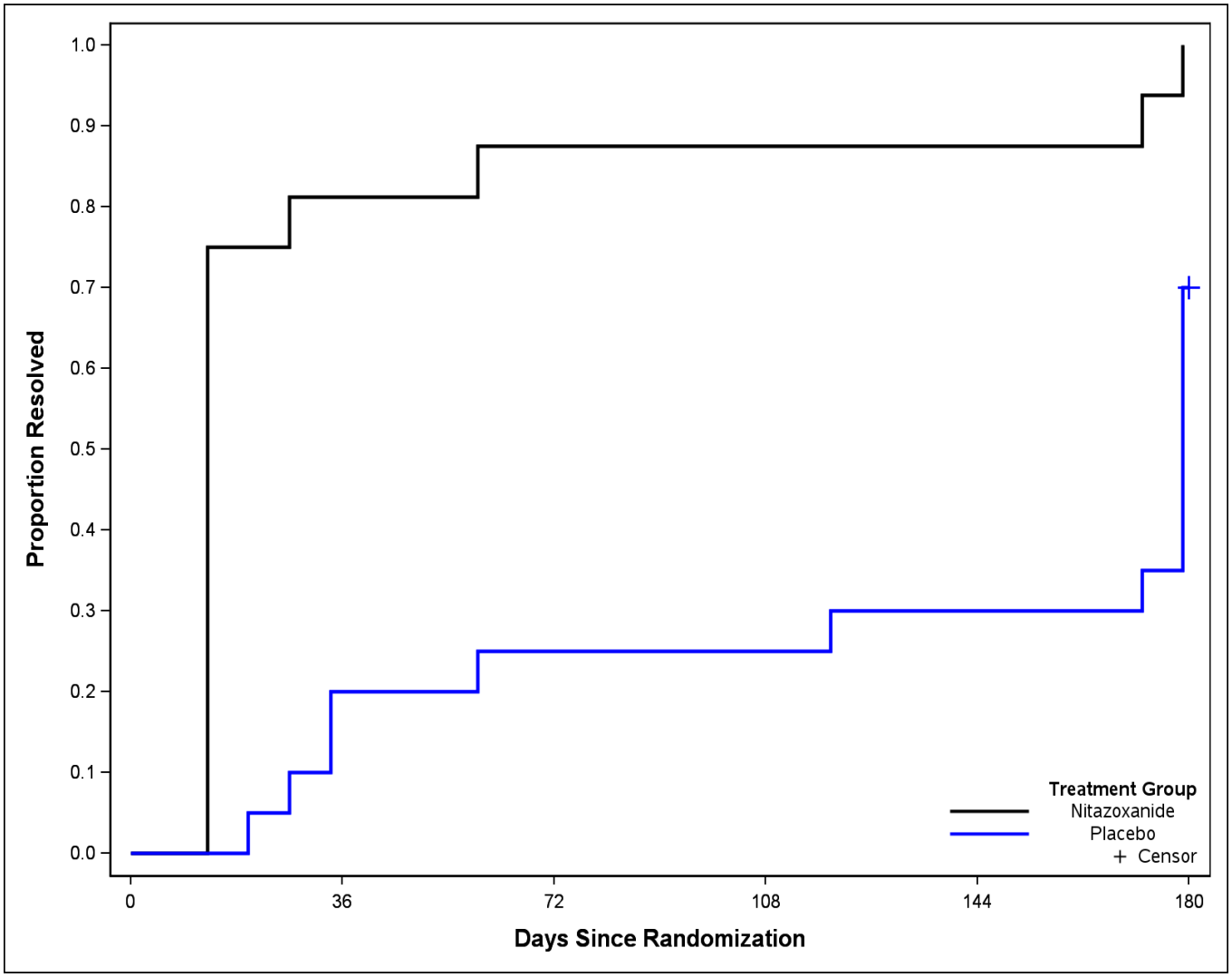
Figure 17: Forest Plot of Change in Viral Titer between Day 1 and Day 180 by Treatment Group and Duration of Symptoms – Norovirus GI, mITT Population

Figure 18: Forest Plot of Change in Viral Titer between Day 1 and Day 180 by Treatment Group and Duration of Symptoms – Norovirus GII, PP Population

Figure 19: Forest Plot of Change in Viral Titer between Day 1 and Day 180 by Treatment Group and Duration of Symptoms – Norovirus GI, PP Population

Figure 20: Kaplan-Meier Curves of Time to Initial Clinical Improvement by Treatment Group – mITT Population

[Implementation Note: Y axis will be "Proportion Improved", x axis will be "Days Since Randomization". Include (N=X) for each group in legend.]



Figures with similar format:

Figure 21: Kaplan-Meier Curves of Time to Cessation of Vomiting by Treatment Group – mITT Population

Figure 22: Kaplan-Meier Curves of Time to No Loss of Appetite by Treatment Group – mITT Population

Figure 23: Kaplan-Meier Curves of Time to Cessation of Diarrhea by Treatment Group – mITT Population

Figure 24: Kaplan-Meier Curves of Time to 50% Reduction in Antimotility Agents by Treatment Group – mITT Population

14.3.1.2 Unsolicited Adverse Events

Figure 25: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity

[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. Each panel represents a treatment group with Nitazoxanide 500 mg on the left and Placebo on the right.]

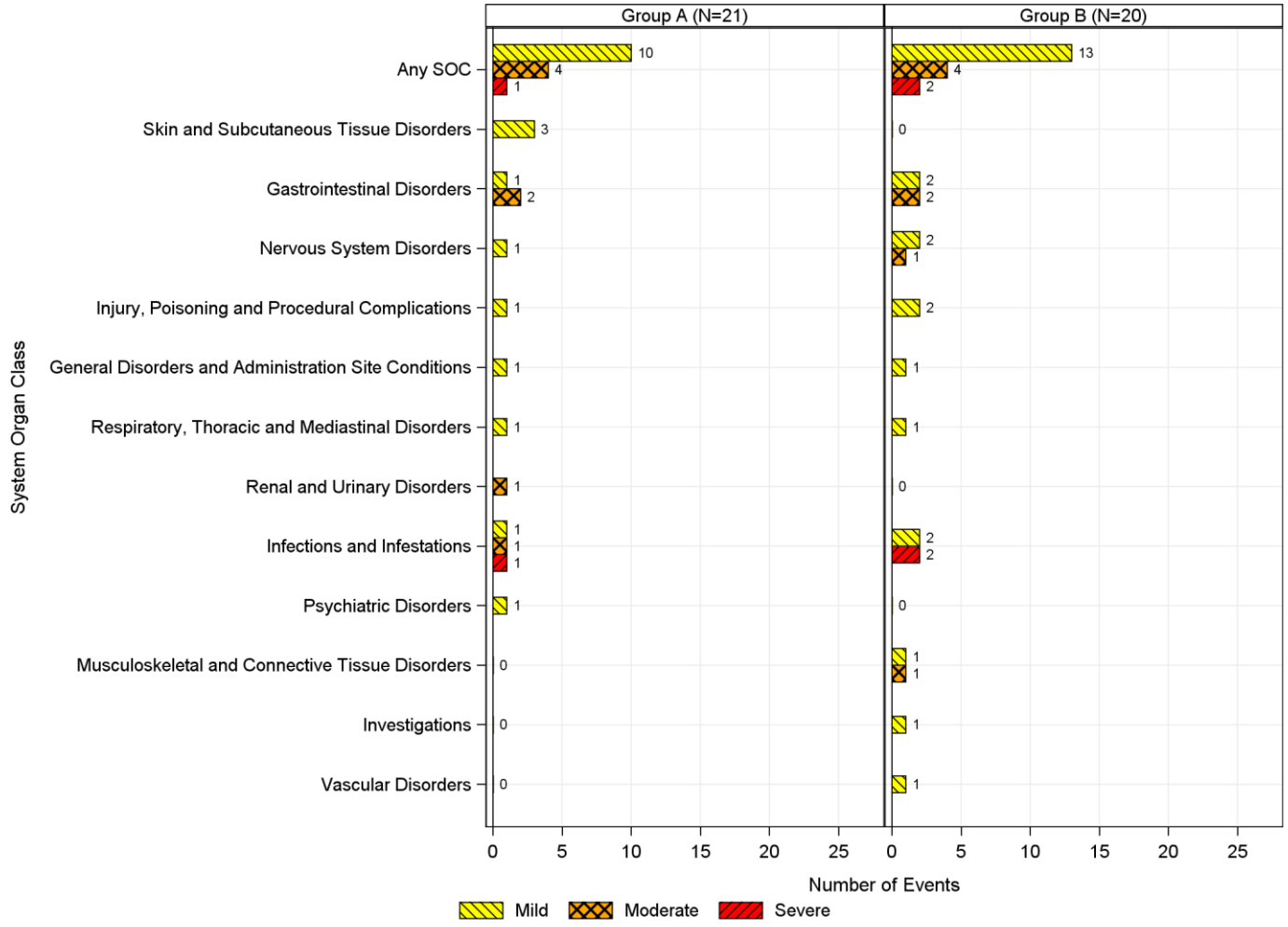
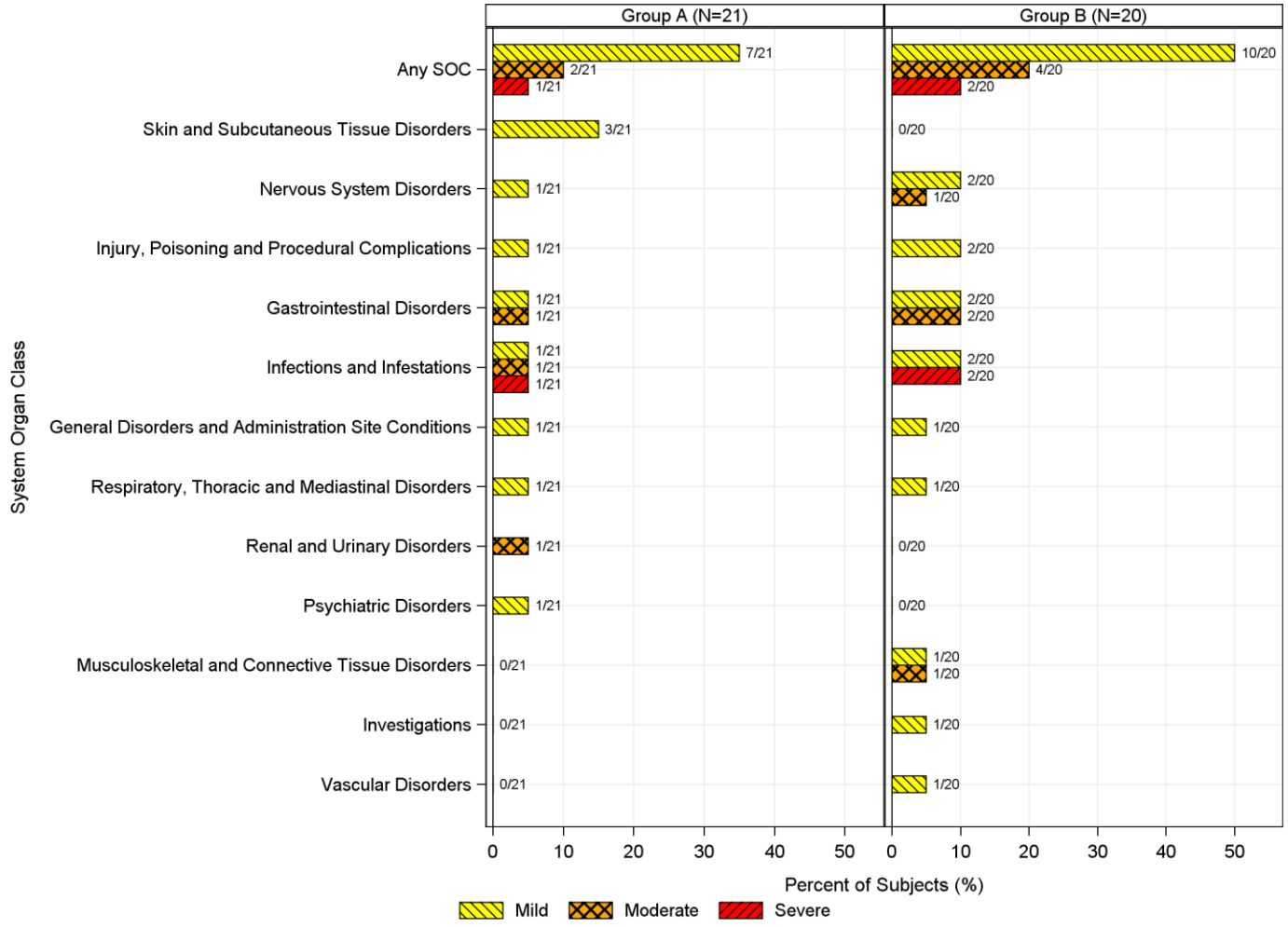


Figure 26: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity

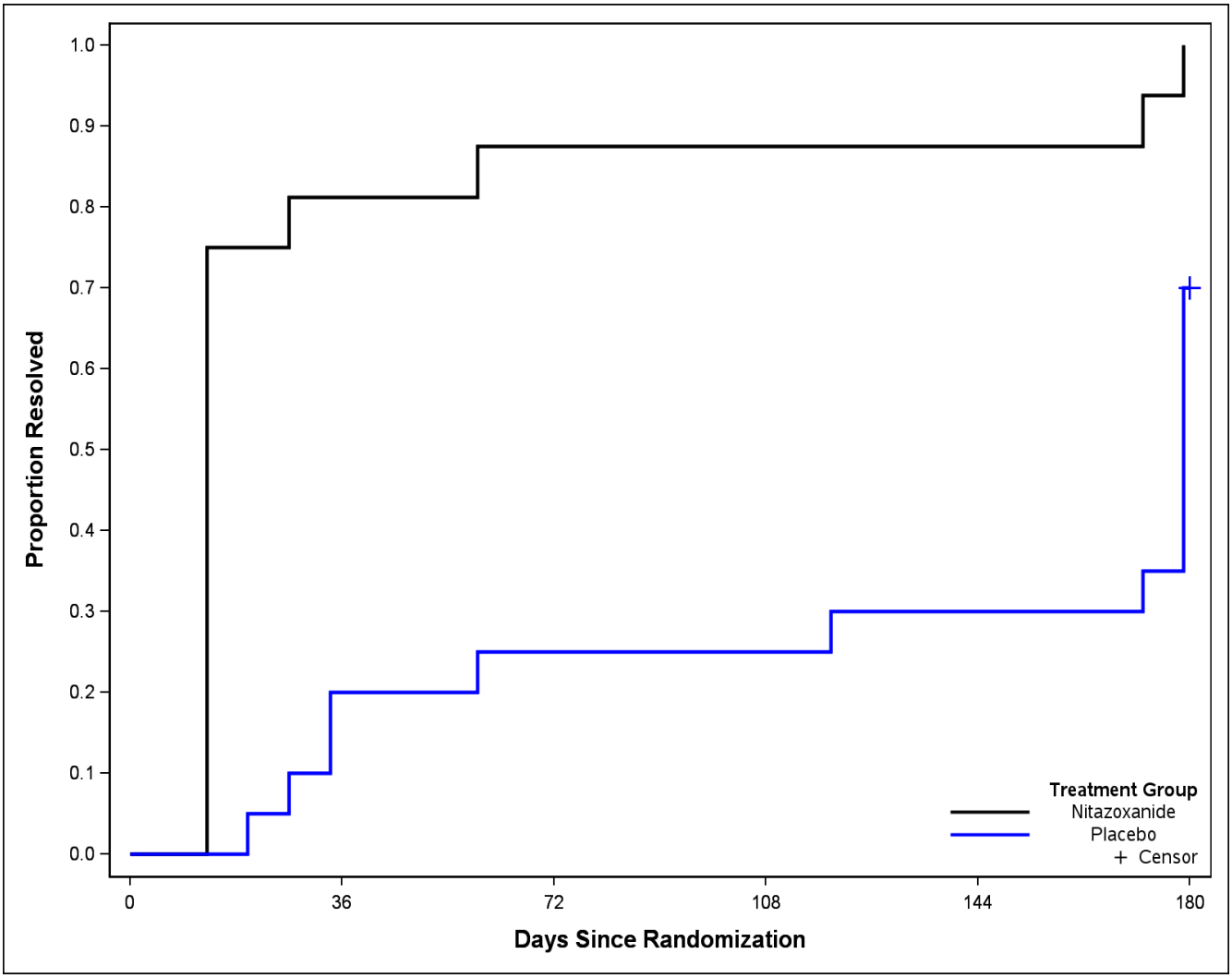
[Implementation note: The figure below is an example only. This figure includes serious and non-serious unsolicited adverse events deemed related to study product. The SOCs will be sorted in descending incidence. Each panel represents a treatment group with Nitazoxanide 500 mg on the left and Placebo on the right.]



14.3.4.4 Displays of Hospitalizations, Allograft Rejection, Graft Loss, Death

Figure 27: Kaplan-Meier Curves of Time to Allograft Rejection by Treatment Group – mITT Population

[Implementation Note: Y axis will be "Proportion Rejected", x axis will be "Days Since Randomization". Include (N=X) for each group in legend.]



Figures with similar format:

Figure 28: Kaplan-Meier Curves of Time to Graft Loss by Treatment Group – mITT Population

[Implementation Note: Y axis will be "Proportion Lost", x axis will be "Days Since Randomization". Include (N=X) for each group in legend.]

Figure 29: Kaplan-Meier Curves of Time to Death by Treatment Group – mITT Population

[Implementation Note: Y axis will be "Proportion Died", x axis will be "Days Since Randomization". Include (N=X) for each group in legend.]

Figure 30: Kaplan-Meier Curves of Time to Withdrawal by Treatment Group – mITT Population

[Implementation Note: Y axis will be "Proportion Withdrawn", x axis will be "Days Since Randomization". Include (N=X) for each group in legend.]

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

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

[Implementation Note: If all subjects received the treatment they were randomized to then a single "Treatment Group" column will be included. Subject ID will be USUBJID (not PATID) for purposes of de-identification.]

Randomized Treatment Group	Actual Treatment Group	Subject ID	Enrollment Date

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 2: 16.2.1: Early Terminations or Discontinued Subjects

[Implementation Note: Category will be "Early Termination" and/or "Treatment Discontinuation." A footnote will be added to indicate the cause of death for any subjects with early termination reason of "Death, not an AE".]

[Implementation Note: Category will be either "Early Termination" or "Treatment Discontinuation." In the "Reason" column, concatenate any "specify" fields, including AE number and DV number. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, alphabetically by Category (in the case a subject both terminates early and discontinues treatment).]

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

Note: EHD.xxxxx: Cause of death was [add cause of death term, if more than one term, separate by commas or "and"].

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Subject-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: Subject refusal." In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, DV Number.]

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

Listing 4: 16.2.2.2: Non-Subject-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: Subject refusal." Sort order: Site, Start Date.]

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

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 5: 16.2.3: Subjects Excluded from Analysis Populations

[Implementation Note: This data in this listing should be congruent with the "Analysis Populations by Treatment Group" table. The reasons included here should match the SAP text that describes who will be excluded from analyses. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: Treatment Group, Subject ID.]

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

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 subject is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)."

For studies in infants and young children, may be more appropriate to use weeks or months for age at enrollment. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: Treatment Group, Subject ID.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	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
- Within 1 month of enrollment
- During study
- If ongoing, display "Ongoing" in the "Condition End Day" column

It may be appropriate to add another category, based on exclusion criteria that restrict conditions within a particular time period (e.g., within 3 years prior to enrollment). In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, MH Number.]

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

16.2.5 Compliance Data

Listing 8: 16.2.5.1: Treatment Compliance Data

[Implementation Note: Each subject will have a single row in the listing. The final pill count column will contain the last pill count entered in the Treatment Dispensing Log. The Dose(s) Missed column will list all doses missed per the subject's daily diary.]

[Implementation Note: Sort order: Treatment Group, Subject ID, Dose Number.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Final Pill Count[a]	Dose(s) Missed[b]
					[e.g., Day 3, Day 3 AM, etc.]

[a] Final pill count will include Day 28 and Day 60 pill counts. Subjects with pill counts at both visits will use the Day 60 pill count as the final pill count.
[b] Dose(s) Missed includes all missed doses per the subject's daily diary. Day X AM = Missed Day X Morning Dose; Day X PM = Missed Day X Evening Dose; Day X = Missed Both Doses on Day X.

Listing 9: 16.2.5.2: Daily Diary Compliance Data

[Implementation Note: Sort order: Treatment Group, Subject ID, Dose Number.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Phase	Week Number	Number of Diaries Missed	Day(s) Missed
				Treatment/Longitudinal			[e.g., Day 3, Day 5, etc.]

Note: Weeks are only included if at least one diary was missed for that week.

Listing 10: 16.2.5.3: Daily Diary Time of Completion Compliance Data – Treatment Phase

[Implementation Note: Sort order: Treatment Group, Subject ID, Dose Number.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Number Completed between 6am and 12pm	Number Completed between 12pm and 6pm	Number Completed between 6pm and 12am	Number Completed between 12am and 6am	Number Completed Less than 12 Hours after Previous Diary Completed

Listing 11: 16.2.5.4: Individual Additional Nitazoxanide Data

[Implementation Note: Additional Doses of Nitazoxanide will be based on records of Nitazoxanide on the concomitant medication form.]

[Implementation Note: In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Number of Days Post Randomization (Duration)	Number of Additional Doses Taken

16.2.6 Individual Efficacy and Immunogenicity Response Data

Listing 12: 16.2.6.1: Individual Treatment Phase Daily Diary Data

[Implementation Note: "Too many" will be listed if number of stools was too many to count. If data is missing, it will be denoted as "—". Rows will not be included for missing diary days. Imputation rules will not be included in the listings. Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Actual Study Day	Number of Bristol Type 6 Stools	Number of Bristol Type 7 Stools	Repeat Dose due to Vomiting	Number of Episodes of Vomiting
					[e.g. 7, Too Many]	[e.g. 7, Too Many]	Yes/No	

Listing 13: 16.2.6.2: Individual Longitudinal Phase Daily Diary Data

[Implementation Note: If data is missing, it will be denoted as "—". Rows will not be included for missing diary days. Imputation rules will not be included in the listings. Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Actual Study Day	Diarrhea (At Least 1 Type 6 or 7 Bowel Movement)	Vomiting
					Yes/No	Yes/No

Listing 14: 16.2.6.3: Weekly Recall Diary

[Implementation Note: If data is missing, it will be denoted as "—". Rows will not be included for missing weeks.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Week Number[a]	Actual Study Day	Average Number Bowel Movements/Day	Average Number Vomiting Episodes/Day	% Type 6 or 7 Stool	% Type 3, 4, or 5 Stool	Abdominal Pain[b]	Urgency to Have Bowel Movement[b]	Fecal Incontinence[b]	Nausea[b]

[a] Week Number is based off of Planned Time Point.
[b] Subjects rated these symptoms as 0 being none and 10 being the worst possible.

Listing 15: 16.2.6.3: Individual PROMIS Scores Data – Quality of Life/PANAS

[Implementation Note: Listing will provide the PROMIS T-scores for IBSQOL. EurQOL Measures will be reported as 'Problems' or 'No Problems'. Positive Affect and Negative Affect will be the reported scores based off of the Definitions in Section 3.3.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Planned Time Point	Actual Study Day	Quality of Life (IBSQOL)	EuroQOL-5 Mobility	EuroQOL-5 Self-Care	EuroQOL-5 Usual Activities	EuroQOL-5 Pain/Discomfort	EuroQOL-5 Anxiety/Depression	EuroQOL-5 Health State	Positive Affect	Negative Affect	EuroQOL-5 Mobility

Listing 16: 16.2.6.5: Individual PROMIS Scores Data – Physical Function, Emotional, and Gastrointestinal Symptoms

[Implementation Note: Listing will provide the PROMIS T-scores for Physical Function, Depression, Anxiety, Fatigue, and GI Symptoms.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Planned Time Point	Actual Study Day	Physical Function	Depression	Anxiety	Fatigue	GI: Diarrhea	GI: Nausea	GI: Fecal Incontinence	GI: Belly Pain

Listing 17: 16.2.6.4: Individual NoV PCR Results Data

[Implementation Note: "N/A" will be listed in the NoV GI PCR Test Result column if NoV GI test not conducted.]

[Implementation Note: Update as appropriate for your study assay/strain and endpoints. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Planned Time Point	Actual Study Day	NoV GII PCR Test Result	NoV GI PCR Test Result

Listing 18: 16.2.6.7: Individual Co-pathogen Status Data

[Implementation Note: Update as appropriate for your study assay/strain and endpoints. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Planned Time Point	Actual Study Day	Co-Pathogen Detected
						[e.g. Norovirus GI/GII, Norovirus GI/GII/Clostridium difficile toxin A/B, None]

Listing 19: 16.2.6.8: Individual Baseline Secretor Status Data

[Implementation Note: Update as appropriate for your study assay/strain and endpoints. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Phenotype Result	Genotype Result
				Secretor/Non-secretor	Secretor/Non-secretor

Listing 20: 16.2.6.9: Individual Serum Immunology Response Data

[Implementation Note: In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Planned Time Point	Actual Study Day	NoV IgA Result	NoV IgG Result	Total IgG Result	NoV IgM Result

Listing 21: 16.2.6.10: Individual Stool Immunology Response Data

[Implementation Note: In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Planned Time Point	Actual Study Day	NoV IgA Result	NoV IgG Result	NoV IgM Result

Listing 22: 16.2.6.8: Individual Chromaturia Data

[Implementation Note: In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Actual Study Day Chromaturia Reported

16.2.7 Adverse Events

Listing 23: 16.2.7.1: 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'. Add columns for MedDRA HLT or LLT depending on halting criteria or other study needs. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, Associated with Dose No., No. of Days Post Associated Dose. If the table will be multi-page, move the footnote/explanation to the footer so that it repeats for each page of the table.]

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

Note: For additional details about SAEs, see Section 14.3.2.

16.2.8 Individual Laboratory Measurements

Listing 24: 16.2.8.1: Clinical Laboratory Results – Chemistry

[Implementation Note: Will include results for Creatinine, Alkaline phosphatase, AST, ALT, BUN, and Total bilirubin.]

[Implementation Note: These listings (for hematology, chemistry, and urinalysis) include all laboratory 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, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort oder: Treatment Group, Subject ID, Laboratory Parameter, and Planned Time Point.]

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

Listing 25: 16.2.8.2: Clinical Laboratory Results – Hematology

[Implementation Note: Will include results for WBC, Hemoglobin, Platelets, Neutrophil, Lymphocyte, Eosinophil, Monocyte, Hematocrit, Mean corpuscular volume.]

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

Listing 26: 16.2.8.3: Clinical Laboratory Results – T-Cell Subsets

[Implementation Note: Will include results for CD3+, CD3+ %, CD4+, CD4+ %, CD8+, CD8+ %.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result

16.2.8.2 Vital Signs

Listing 27: 16.2.8.2.1: Vital Signs

[Implementation Note: This listing includes all vital sign assessments, scheduled and unscheduled. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Planned Time Point	Actual Study Day	Temperature (°F)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Weight (kg)	Height (cm)

Listing 28: 16.2.8.3.1: Hospitalizations

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	No. of Days Post Randomization (Duration)	Diagnosis	Reason for hospitalization	Discharge Status	MedDRA System Organ Class	MedDRA Preferred Term

Listing 29: 16.8.3.2: Individual Graft Loss or Rejection Data

[Implementation Note: In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Listing should be sorted by Treatment Group, Subject ID, Planned Time Point. If no resolution date, duration should be listing as ONGOING.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Number of Days Post Randomization (Duration)	Event Type
					Graft Loss/Graft Rejection

Listing 30: 16.8.3.3: Deaths

[Implementation Note: Cause of Death will be listed as the Cause of Death on the CRF. If multiple causes listed, Cause of Death field will be populated as "Primary/Secondary/Tertiary/Quaternary/Quinary". Listing should be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Number of Days Post Randomization	Cause of Death
					Primary/secondary/etc.

16.2.8.4 Physical Exam Findings

Listing 31: 16.2.8.4.1: Physical Exam Findings

[Implementation Note: This listing includes all physical exam findings, scheduled and unscheduled. If a subject 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, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.8.5 Concomitant Medications

Listing 32: 16.2.8.5.1: 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, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, and CM Number.]

Treatment Group	Subject ID	Transplant Type	Duration of Symptoms	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for the treatment of Norovirus?	ATC Level 1 (ATC Level 2)

16.2.8.6 Pregnancy Reports

Listing 33: 16.2.8.6.1: Pregnancy Reports – Maternal Information

[Implementation Note: Only include the "Pregnancy Number" column if a subject 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, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, Pregnancy Number.]

`	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.											

Listing 34: 16.2. 8.6.2: Pregnancy Reports – Gravida and Para

			Live Births												
Subject ID	Pregnancy Number	Gravida	Extremely PB[a]	Very Early PB[a]	Early PB[a]	Late PB[a]	Early TB[b]	Full TB[a]	Late TB[a]	Post TB[a]	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															
[a] Term Birth															

Listing 35: 16.2. 8.6.3: Pregnancy Reports – Live Birth Outcomes

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

Listing 36: 16.2. 8.6.4: Pregnancy Reports – Still Birth Outcomes

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

Listing 37: 16.2. 8.6.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

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