Statistical Analysis Plan

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SBH-OEV-131-Statistical Analysis Plan (SAP) Approval Signatures

(CRO)	Date
Signature:	
Printed Name:	
Organization and Title: Sr. Global Project Manager - CRO	
Signature:	
Printed Name:	
Organization and Title: Statistician – CRO	
Johns Hopkins University (JHU)	**Date**
Signature:	
Printed Name:	
Organization and Title: Principal Investigator – JHU	
Scandinavian Biopharma Holding AB (SBH)	**Date**
Signature:	
Printed Name:	
Organization and Title: Medical Advisor - SBH	
Signature:	
Printed Name:	
Organization and Title: Statistician - SBH	

SBH-OEV-131-Statistical Analysis Plan Revision History

The SAP will be reviewed after each system update as applicable, protocol amendment and/or changes to the scope of statistical tasks. An annual review must occur if none of the other review parameters are met.

Version #	Date	Revision Summary
1.0	14JUN2024	Initial Plan

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
C	Celsius
cfu	Colony-forming units
CHIM	Controlled Human Infection Model
CI	Confidence Interval
CIR	Center for Immunization Research
CRF	Case Report Form
CSR	Clinical Study Report
dmLT	Double mutant Heat-Labile Toxin
E. coli	Escherichia coli
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
ETEC	Enterotoxigenic Escherichia coli
F	Fahrenheit
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IV	Intravenous
LCTBA	Recombinant hybrid protein between B-subunit Heat Labile Toxin from E. coli and Cholera Toxin B subunit
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
N	Number (typically refers to Subjects)
PI	Principal Investigator
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedures
U	Units
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Purpose and Structure of the Document

The Statistical Analysis Plan (SAP) for "Pre-Study of wild type Enterotoxigenic E. coli (ETEC) Strain for Verification of a planned Challenge Dose" (Protocol OEV-131) describes and expands upon the statistical information presented in the protocol.

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

This document covers five broad components of the analysis plan: (1) a description of the purpose(s) and timing(s) of analyses; (2) a description of the study design, its objectives, and the variables collected/assessed to be used in analyses; (3) general statistical principles; (4) comprehensive statistical analysis methods for study outcomes, and (5) a list of proposed tables and figures along with mock-ups (Appendices).

1.2. Purpose of the Analyses

This study aims to estimate the incidence of moderate and severe diarrhea among subjects challenged with 4x109 cfu of the E. coli E24377A strain, as well as assess the safety of the E24377A dose. This dose is planned to be used in a subsequent challenge study of the clinical efficacy of an oral ETEC vaccine (ETVAX®):

2. INVESTIGATIONAL PLAN

2.1. Overall Study Design and Plan

This is an open label study with the aim to estimate the incidence of moderate and severe diarrhea among subjects challenged with 4x109 cfu of the E. coli E24377A strain. This dose is planned to be used in a subsequent challenge study of the clinical efficacy of an oral inactivated tetravalent enterotoxigenic Escherichia coli (ETEC) vaccine with LCTBA and dmLT (ETVAX®).

The study will be conducted at one site: the Center for Immunization Research (CIR), Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, United States.

Up to 30 subjects will be enrolled and challenged with approximately 4x109 cfu of the ETEC E24377A strain.

The study will consist of three study periods: screening, inpatient period, and outpatient follow-up. Subjects will be evaluated for study eligibility during the screening period. After provision of written informed consent, subject eligibility for study entry will be assessed. Subjects who have been assessed to be eligible for the study, based on screening evaluations, will be admitted to the in-patient unit on Day -1, the day before E24377A administration, for study orientation and to be monitored for any signs and symptoms of illness. At baseline (Day 1), subjects who remain eligible and are willing to participate will be enrolled in the study and receive a single administration of E24377A.

Subjects may remain in the in-patient unit until they meet discharge criteria. Routine discharge is scheduled for 8 days after challenge (Day 9), dependent upon 2 consecutive negative stool culture results. During the in-

patient period, subjects will be examined daily for signs and symptoms of ETEC illness. Vital signs will be measured at least 3 times daily starting on Day 1, and postural blood pressure and pulse will be measured as needed. All stools will be collected and evaluated, weighed, and graded by the study staff. Up to 3 stools and/or rectal swabs collected each day will be cultured.

If the subject develops any symptom suggestive of diarrhea, they will be encouraged to drink liquids. If a subject vomits or is unable to consume an adequate volume of liquids, then intravenous (IV) fluids may be administered.

In order to reduce the risk of secondary infection after discharge, all subjects will receive a 3-day course of antibiotics. The subject will begin a 3-day course of ciprofloxacin 500 mg by mouth twice daily (or azithromycin 500 mg by mouth daily for three days, or amoxicillin 500 mg by mouth three times daily for three days if the subject was allergic to or unwilling to take ciprofloxacin) on the morning of Day-6, or sooner if the subject has met the criteria for early antibiotic treatment.

Subjects will be discharged from the in-patient unit if determined eligible for discharge (2 stools negative for the challenge organism by culture, having received at least 2 doses of antibiotics, with improvement or resolution of symptoms). Subjects who meet the criteria for early antibiotic treatment, may be discharged from the in-patient unit prior to Day 9.

After discharge from the in-patient unit, all subjects will attend the scheduled follow-up visit/contact on an out-patient basis on Day 29 (physical visit) and Day 180 (phone).

2.2. Study Objectives and Endpoints

2.2.1. Primary Objectives and Endpoints

Primary Objective	Primary Endpoint
• To evaluate the moderate and severe diarrhea attack rate after challenge with wild type enterotoxigenic *E. coli* (ETEC) strain E24377A	• Moderate and severe diarrhea, as defined by ≥ 4 grade 3-5 stools or > 400 grams of grade 3-5 stools passed within a rolling 24-hour period, deemed attributable to ETEC. Diarrhea episodes or ETEC symptoms beginning any time after challenge through 120 hours post-challenge may contribute toward the primary endpoint and will be followed to resolution. The end of a diarrheal episode occurs when a subject does not pass any grade 3-5 stool within 24 hours. An adjudication committee will be used to judge if the diarrhea is attributable to ETEC and determine if a participant meets the primary endpoint by considering individual data as described in the adjudication charter. Stool grading criteria: grade 1 = firm, formed; grade 2 = soft but still formed; grade 3 = thick liquid; grade 4 = thin liquid; grade 5 = clear or translucent, watery

2.2.2. Secondary Objectives and Endpoints

Secondary Objectives	Secondary Endpoints
Clinical/Microbiology Objective: • To further evaluate the clinical features of the challenge with wild type ETEC strain E24377A	**Clinical Endpoints:** • Severe diarrhea defined as ≥6 grade 3-5 stools or >800g of grade 3-5 stools passed within a rolling 24-hour period. • ETEC disease severity: 3-component disease score (total score) utilizing objective signs, subjective symptoms, and stool output. • Incidence of diarrhea (≥2 grade 3-5 stools in a 24-hour period) of any severity. • Total weight of grade 3-5 stools passed per subject over the 120-hour observation period. • Number of grade 3-5 stools per subject over the 120-hour observation period. • Occurrence of other ETEC Disease-specific events (malaise, loss of appetite, headache, chills, fever, nausea, abdominal pain, abdominal cramps, myalgia, arthralgia, urgency of defecation, vomiting and lightheadedness). • Self-assessment of ETEC illness impact on daily activity at Day 6. • Time (relative to challenge) to the first grade 3-5 stool of the first diarrhea episode. • Time (relative to challenge) to meeting the primary endpoint (time of the stool that meets the criteria for at least moderate diarrhea). • Requirement of early (prior to Day 6) antibiotic treatment. • Requirement of IV fluids. • Maximum 24-hour grade 3-5 stool output (weight). • Maximum number (24-hour) of grade 3-5 stools. **Microbiology Endpoint:** • Qualitative shedding of the E24377A challenge strain post-challenge (positive or negative).
Safety Objective: • To evaluate the safety of the challenge with wild type ETEC strain E24377A	**Safety Endpoints:** • Adverse events leading to study withdrawal. • Serious adverse events (SAEs) occurring during the 6 months of the study (from the time of challenge).

2.2.3. Exploratory Objectives and Endpoints

Exploratory Objectives	Exploratory Endpoints
Immunogenicity Objective: • To evaluate immunogenicity of the challenge with wild type enterotoxigenic *E. coli* (ETEC) strain E24377A	**Immunogenicity Endpoints that may be conducted:** • Serum IgA and IgG antibody seroconversion (≥2-fold increase over baseline to challenge strain specific antigens LT, CS1, CS3 in serum) from baseline prior to challenge and post-challenge. In addition, ≥4-fold increase may be explored. • Increases in serum IgA measurements utilizing Antibody in the Lymphocyte Supernatant (ALS) assay in response to LT, CS1, and CS3. • Increase in Memory B cell measurements utilizing Antibody in the Lymphocyte Supernatant (ALS) assay. • Whole blood for transcriptomics. • Increases in Fecal IgA levels to LT, CS1, CS3 from baseline prior to challenge and post-challenge. • Biomarker assessments to measure intestinal inflammation in stool (e.g., calprotectin, neopterin, myeloperoxidase). • Biomarker assessments to measure systemic inflammation in serum (e.g., C-reactive protein, Intestinal Fatty Acid binding protein). • Fecal microbiome assessment.
Microbiology Objective: • To evaluate the level of quantitative fecal shedding (colony forming units per gram of stool) of the E24377A challenge strain post-challenge	**Microbiology Endpoint:** • Number of colony forming units (cfu) per gram of stool of the E24377A challenge strain on Days 2 and 4 after challenge.

2.3. Study Schedule

Table 1 presents the schedule of study visits and assessments.

Table 1: Schedule of Events

	Study Specific Screen	Inpatient Period										Outpatient Visit	Phone Call
Study Day	**Scr -60 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**29**	**180**
Informed Consent and Comprehension Test	X												
Demographics	X												
Inclusion/Exclusion Criteria	X	X	X										
Medical History	X	X											
Functional Bowel Survey	X												X
Full Physical Exam	X	X											

	Study Specific Screen	Inpatient Period										Outpatient Visit	Phone Call
Study Day	**Scr -60 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**29**	**180**
Focused Physical Exam			X	X	X	X	X	X	X	X	X	(X)[1]	
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	
Serology (HIV, HBsAg, and HCV)	X[3]												
Hematology	X	X[4]											
Clinical Chemistry	X	X[4]											
IgA deficiency screen	X[3]												
Serum HCG Pregnancy Test[5]	X	X											
Urine Drug Screen	X												
Urine Pregnancy Test[5]			(X)									X	
Enrollment			X										
E24377A challenge			X										
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Interim Medical Interview[6]			X	X	X	X	X	X	X	X	X	X	X
AE			X	X	X	X	X	X	X	X	X	X	
SAE/AESI			X	X	X	X	X	X	X	X	X	X	X
Antibiotic therapy								X[7]	X	X			
Stool collection for weighing and grading[8]			X	X	X	X	X	X	X	X	X		
Stool culture			X	X[9]	X	X[9]	X	X	X	X	X		
Serum Sample for Immunogenicity		X	(X)[10]	X	X					X		X	
Whole blood for ALS		X	(X)[10]		X				X				
Fecal sample for immunogenicity		X	(X)[10]	X	X	X			X	X		X	
Follow-Up Telephone Contact													X
ETEC Impact on ADLs								X					

Note: (X) denotes optional event or procedure

[1] Physical exam on Day 29 optional if there are symptoms.

[2] Pulse, sitting, lying or standing blood pressure and temperature will be measured at least 3 times daily starting on Day 1. In addition, postural blood pressure and pulse will be measured if suspicion or evidence of hypovolemia (based on assessment by clinician). Vital signs may be measured more frequently if the subject is ill.

[3] Must be collected from Day -30 to Day -2

[4] Hematology and clinical chemistry will be performed at Day -1 if not performed within the previous 7 days.

[5] Serum HCG pregnancy tests will be performed for people of child-bearing potential. Urine HCG will be done if serum results from admission day (Day -1) are not available.

[6] During the inpatient and outpatient phases of the study, the interview will be used to update baseline medical history, monitor safety, and to confirm ongoing eligibility.

[7] Subjects meeting the criteria for early antibiotic treatment per the discretion of an investigator may start this treatment prior to Day 6.

[8] Weighing and grading ends once subject has two consecutive ETEC negative cultures, unless there is a clinical indication to continue.

[9] Quantitative stool cultures (cfu per gram of stool) will be collected on Days 2 and 4.

[10] To be collected before challenge if not taken on Day -1.

2.4. Statistical Considerations for the Study Design

2.4.1. Sample Size Considerations

In preparation for a planned phase 3 vaccination and CHIM study, it is assumed based on previous clinical experience, that a pre-study in up to 30 subjects should be sufficient to estimate the incidence of moderate and severe diarrhea among subjects challenged with 4x109 cfu of the E. coli E24377A strain. With 25 subjects and an attack rate of 60% or 72%, the 95% Clopper-Pearson confidence interval for the estimated incidence would be (0.39, 0.79) or (0.51, 0.88), respectively.

Since there is a maximum capacity of 30 subjects for the in-patient period, the number of subjects will not exceed 30.

2.4.2. Allocation of Subjects to Study Arms

Not applicable, as this is a single-arm study.

2.4.3. Blinding

Not applicable, as this is an open label study.

2.5. Study Definitions and Derived Variables

2.5.1. Diarrhea

Each stool will be graded according to the following scale:

Grade 1 = firm, formed
Grade 2 = soft but still formed
Grade 3 = thick liquid
Grade 4 = thin liquid
Grade 5 = clear or translucent, watery

A loose stool is defined as a grade 3-5 stool.
Diarrhea is defined as passing at least 2 loose (grade 3-5) stools within a 24-hour period. Diarrhea severity is assigned according to the following scale:

Mild	2-3 grade 3-5 stools in 24 hours and ≤400 grams of grade 3-5 stools passed in a 24-hour period
Moderate	4-5 grade 3-5 stools in 24 hours or >400-800 grams of grade 3-5 stools passed in a 24-hour period
Severe	≥6 grade 3-5 stools in 24 hours or >800 grams of grade 3-5 stools passed in a 24-hour period

A diarrhea episode starts when the first grade 3-5 stool that contributes to diarrhea of any severity is passed. A diarrhea episode ends when a subject has not passed any grade 3-5 stools within the preceding 24 hours. A rolling 24-hour window will be used to determine the severity of diarrhea. At the time of each grade 3-5 stool passing, all grade 3-5 stool output during the previous 24 hours will be assessed against the diarrhea severity scale, and a severity will be assigned to that 24-hour window. Due to this rolling window, multiple 24-hour windows may be assessed, and multiple diarrhea severity thresholds may be met during a single diarrhea episode. The maximum severity of diarrhea met during a diarrhea episode will be considered the severity of that episode.

2.5.2. Primary Endpoint

An adjudication committee will determine whether each subject has met the primary endpoint. Primary endpoint determinations for each subject will be based on the majority vote of the adjudication committee as described in the adjudication charter.

2.5.3. Unadjudicated Primary Endpoint

The unadjudicated primary endpoint, defined only by objective stool output criteria without adjudicator input, will be assessed as a sensitivity analysis. The unadjudicated primary endpoint is defined as ≥ 4 grade 3- 5 stools or > 400 grams of grade 3-5 stools passed within a rolling 24-hour period. Diarrhea episodes beginning any time after challenge through 120 hours post-challenge may contribute toward the unadjudicated primary endpoint.

2.5.4. Time to Event

2.5.4.1. Time to Primary Endpoint

The secondary clinical endpoint, time to meeting the primary endpoint, is defined as the number of hours between challenge and the first grade 3-5 stool that passes the frequency or weight threshold of moderate diarrhea, occurs within a diarrhea episode that began prior to 120 hours post challenge, and is deemed attributable to ETEC by an adjudication committee. Subjects who did not meet the primary endpoint will be censored at 120 hours post challenge.

Some subjects whose measured stools did not meet the frequency or weight thresholds for moderate or severe diarrhea may still meet the primary endpoint according to the adjudication committee. In the time to primary endpoint analysis, such subjects will be considered to have met the primary endpoint at time of antibiotic administration. As a sensitivity analysis, these subjects will be considered to have met the primary endpoint at 120 hours post challenge.

2.5.4.2. Time to Unadjudicated Primary Endpoint

Time to meeting the unadjudicated primary endpoint is defined as the number of hours between challenge and the first grade 3-5 stool that passes the frequency or weight threshold of moderate diarrhea and occurs within a diarrhea episode that began prior to 120 hours post challenge. Subjects who did not meet the unadjudicated primary endpoint will be censored at 120 hours post challenge.

2.5.4.3. Time to Diarrhea Onset

The secondary clinical endpoint, time to onset of diarrhea, is defined as the number of hours between challenge and the first grade 3-5 stool of a subject's first diarrhea episode during the inpatient period. Subjects who experienced no diarrhea episodes during the inpatient period will be censored at 120 hours post challenge.

2.6. Clinical Variables

2.6.1. Stool Output

Every stool passed during the inpatient period (Day 1 through up to Day 9) will be collected. Clinic staff will grade each stool according to the scale in Section 2.5.1 Time of stool (hour and minute), stool weight (grams), and stool grade (Grade 1 through Grade 5) will be recorded and used to determine whether diarrhea occurred according to the definitions in Section 2.5.1.

2.6.2. ETEC Disease Severity Score

ETEC disease severity will be assessed according to a three-component disease score consisting of objective signs (vomiting frequency and fever), subjective symptoms (lightheadedness, nausea, malaise, headache, and abdominal cramps), and stool output (maximum number and weight of grade 3-5 stools during a 24-hour period), all measured regularly throughout the entire inpatient period (see Section 2.3 for schedule of events).

See Table 2 for specific ETEC disease severity scoring criteria. Scores may range from 0 (no diarrhea and no other signs or symptoms of ETEC disease) to 8 (severe ETEC disease). One score will be assigned to each subject based on the maximum severity of each scoring component during the inpatient period.

Table 2: ETEC Disease Severity Score Components

Parameter	Outcome	Score
Objective signs	>1 episode of vomiting/24 hours OR any fever	2
	1 episode of vomiting AND no fever	1
	No vomiting AND no fever	0
Subjective symptoms	Moderate-severe light-headedness OR Severe nausea, malaise, headache or abdominal cramps	2
	Mild light-headedness OR Mild-moderate nausea, malaise, headache or abdominal cramps	1
	No 'subjective symptoms'	0
Diarrhea score	>1000 grams of grade 3-5 stool OR >12 grade 3-5 stools in 24 hours	4
	>600 to ≤1000 grams of grade 3-5 stool OR >7 to 12 grade 3-5 stools in 24 hours	3
	>400 to ≤600 grams of grade 3-5 stool OR >4 to ≤7 grade 3-5 stools in 24 hours	2
	>0 to ≤400 grams of grade 3-5 stool OR 1 to 4 grade 3-5 stools in 24 hours	1
	No grade 3-5 stools	0

1 gram of grade 3-5 stool is considered equivalent to 1 mL of grade 3-5 stool.
Fever is defined as ≥38.0°C or ≥100.4°F.

2.6.3. ETEC Impact on Activities of Daily Living (ADLs)

On Day 6, subjects will answer the following two questions:

1. If traveling for vacation or business, would you have changed your itinerary?
    - Subjects will report "Yes" or "No".
2. Would you have stayed in bed (if so, how long)?
    - Subjects will report "Yes" or "No". If a subject reports "Yes", they will also report the amount of time they would have stayed in bed in hours and minutes.

2.6.4. Early Antibiotic Treatment

On the morning of Day-6, all subjects will start a 3-day course of antibiotics except those who meet at least one of the criteria for early antibiotic treatment, which include the following:

- Severe diarrhea as defined as >800 grams of grade 3-5 stools within a rolling 24 hour-period.
- Stool output consistent with moderate diarrhea for 48 hours.
- Diarrhea of any severity AND 2 or more of the following symptoms: severe abdominal pain, severe abdominal cramps, severe nausea, severe headache, severe myalgias, severe arthralgia), any fever (≥ 100.4°F, 38.0°C), or any vomiting.
- Any fever ≥ 102.1°F (39.0°C).
- A study clinician determines early treatment is warranted for any other reason.

Subjects who meet any criterion for early antibiotic treatment will start antibiotic treatment at the time of meeting the criterion. These subjects may be discharged from the inpatient unit earlier than anticipated upon meeting all discharge criteria. Discharge criteria include passing at least 2 stools negative for the challenge organism, having taken at least 2 doses of antibiotics, and having improvement or resolution of ETEC symptoms.

2.6.5. Requirement of IV Fluids

A subject may be administered IV fluids if they experience any of the following conditions:

- Abrupt onset of loose/liquid stool of >300 g, or >400 g of loose/liquid stools over 2 hours in conjunction with other symptoms, as determined by PI or designee.
- Hypovolemia, defined as confirmed supine systolic blood pressure (BP) < 90 mmHg and associated symptoms, or significant light-headedness on standing, with a confirmed postural change in BP or pulse.
- A decrease in systolic BP or diastolic BP of > 20 mmHg or increase in pulse of > 30 beats/minute takes place when measured lying down vs. two minutes after standing.
- If determined necessary by the study provider, e.g., diarrhea with nausea/vomiting and unable to drink enough to keep up with output, or other reason.

2.6.6. Functional Bowel Disorder Survey

The Functional Bowel Survey is an adaptation of Rome III guidelines utilized by the CIR to screen for gastrointestinal dysfunction per the CIR guideline. The Functional Bowel Disorder Survey will be completed by subjects at screening and at Day 180.

2.7. Microbiology Variable

2.7.1. Qualitative Shedding of Challenge Strain

Up to 3 fecal samples per subject per day of the inpatient period will be cultured for presence of the E24377A challenge strain. If no stool is passed, rectal swabs may be collected and cultured. Culture results will be reported as positive or negative for E24377A.

2.8. Safety Variables

2.8.1. Medical History

Medical history will be obtained at screening in order to verify that the eligibility criteria are met. Medical records will not be requested unless there is a need to clarify a question in the participant's medical history or if the participant had an intercurrent illness or injury requiring medical care during the study.

2.8.2. Prior and Concomitant Medications

Medications taken by the subjects within 28 days prior to study screening until the follow-up visit (Day 29) will be collected. Medication that was stopped before baseline (Day 1) will be classified as 'prior medication'. Medications used on or after Day 1 will be classified as 'concomitant medication'.

2.8.3. ETEC Disease-Specific Solicited Events

ETEC disease-specific solicited events will be collected throughout the inpatient period. Between challenge

and discharge, these pre-defined solicited events will be reported as adverse events, with severity reported by subjects and relationship to the challenge strain, study procedures, and/or antibiotics determined by the PI or designee.

2.8.3.1. Subjective ETEC Disease-Specific Solicited Events

The following subjective ETEC disease-specific symptoms will be solicited from subjects during daily inpatient physical examinations:

- Malaise
- Loss of appetite
- Headache
- Chills
- Nausea
- Abdominal pain
- Abdominal cramps
- Myalgia
- Arthralgia
- Urgency of defecation
- Lightheadedness

The Investigator will assess the severity of these subjective symptoms using his/her clinical expertise and judgement according to Table 3.

Table 3: Grading Scale for Unsolicited Adverse Events and Subjective ETEC-Specific Solicited Events

Severity	Definition
Mild	(Grade 1) The AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.
Moderate	(Grade 2) The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.
Severe	(Grade 3) The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the subject.
Potentially Life-Threatening	(Grade 4) Potentially life-threatening event.

2.8.3.2. Objective ETEC Disease-Specific Solicited Events

The following objective ETEC disease-specific symptoms will be documented as they occur during the inpatient period:

- Diarrhea
- Fever
- Vomiting
- Hypovolemia

The severity of diarrhea, fever, and vomiting will be assigned according to Table 4.
Hypovolemia is defined as confirmed supine systolic blood pressure (BP) < 90 mmHg and associated symptoms, or significant light-headedness on standing, with a confirmed postural change in BP or pulse. The Investigator will determine whether hypovolemia is present using his/her clinical expertise and judgement. Hypovolemia will not be graded for severity.

Table 4: Grading Scale for Objective ETEC-Specific Solicited Events

Event	Severity[a]	Parameter
Diarrhea, based on highest output of grade 3-5 stools in any 24-hour period. (A diarrhea episode ends when there is a 24-hour window with no grade 3-5 stools.)	1	Mild: 2-3 grade 3-5 stools in 24 hours and ≤400 grams of grade 3-5 stools passed in a 24-hour period
	2	Moderate: 4-5 grade 3-5 stools in 24 hours or >400-800 grams of grade 3-5 stools passed in a 24-hour period
	3	Severe: ≥6 grade 3-5 stools in 24 hours or >800 grams of grade 3-5 stools passed in a 24-hour period
	4	Potentially life-threatening
Fever [b]	1	100.4°F–101.1°F (38.0–38.4°C)
	2	101.2°F–102.0°F (38.5–38.9°C)
	3	102.1°F–104°F (39.0–40.0°C)
	4	>104°F (>40.0°C)
Vomiting	1	One episode within a 24-hour period
	2	Two episodes within a 24-hour period
	3	More than two episodes within a 24-hour period
	4	Potentially life-threatening consequence of emesis

[a] 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Potentially life-threatening.
[b] Oral temperature; no recent hot or cold beverages, eating or physical activity. If temperature is ≥ 100.4 °F every attempt should be made to repeat within 20 minutes. If the repeat temperature is WNL and the investigator feels the repeated temperature is a more accurate reflection of the subject's real temperature a fever will not be entered into the eCRF.

2.8.4. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal values from relevant tests, such as vital signs), symptom, or disease temporally associated with the use of an investigational product, regardless of whether it is considered related to the investigational product.

In this study, the challenge strain is considered to be an investigational product and the causal relationship to the ingestion of the challenge strain will be assessed. In addition, the causal relationship between an AE and treatment with antibiotics (not an investigational product) and/or study procedures will be assessed.

Severity of AEs will be assessed according to Table 3.

Serious Adverse Events

A serious adverse event (SAE) is any AE that:

- Results in death;
- Is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization[1];
- Results in persistent or significant disability/incapacity[2];
- Is a congenital anomaly/birth defect[3];
- Is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent any of the SAEs defined above).

[1]The subject has spent significant time, usually involving at least an overnight stay, at the hospital or emergency room for treatment that would not have been appropriate in a primary care office or outpatient setting.
[2]There is a substantial disruption of the subject's ability to carry out normal life functions.
[3]Abortion, stillbirth and any malformation/disease must be reported as an SAE.

Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. The development of Irritable Bowel Syndrome or other continuing gastrointestinal condition will be considered an AESI.

Serious Adverse Reactions

The term serious adverse reaction (SAR) is to be used whenever the Investigator assessed the SAE as possibly or probably related to the investigational product. In this study the challenge strain is considered to be an investigational product and the causal relationship to the ingestion of the challenge strain will be assessed.

Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is any SAR whose nature or intensity is not consistent with the current version of the Investigator's Brochure (IB).

2.8.5. Vital Signs

Systolic and diastolic blood pressure (mmHg), pulse (beats/minute) and temperature (□C), will be measured at least 3 times daily during in-patient period. In addition, postural (supine to standing) blood pressure and pulse will be measured if indicated by clinical signs and symptoms. If tolerated, postural vital signs will be measured after the subject has been supine for 2 minutes, then again after 2 minutes of standing. Vital signs may be measured more frequently if the subject is ill or per the orders of the PI or designee.

Vital signs will be graded according to Table 5.

Table 5: Grading Scale for Vital Signs Parameters

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Tachycardia (beats/minute)	101–115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia (beats/minute)	50-54[a]	45–49	<45	ER visit or hospitalization for rrhythmia
Fever (°C) (°F)	38.0–38.4 100.4–101.1	38.5–38.9 101.2–102.0	39.0-40 102.1- 104	>40 >104
Hypertension (systolic, mm Hg)	141–150	151 – 155	>155	ER visit or hospitalization for hypotensive shock
Hypertension (diastolic, mm Hg)	91–95	96 – 100	>100	ER visit or hospitalization for hypotensive shock
Hypotension (systolic, mm Hg)[b]	85–89	80 – 84	<80	ER visit or hospitalization for hypotensive shock

[a] Grade 1 bradycardia will not be considered an abnormality for this study unless judged to be clinically significant by the PI.
[b] If a subject has a baseline systolic BP in the 90's then a decrease in BP < 10 without associated clinical symptoms will not be considered an abnormality for this study unless judged to be clinically significant by the PI.

2.8.6. Hematology and Chemistry

Blood samples will be collected for clinical laboratory evaluations during screening. Blood samples for clinical laboratory evaluations will also be collected at Day -1 if they were not performed within the previous 7 days.

Clinical hematology laboratory evaluations will include measures of hemoglobin, hematocrit, white blood cell count with differential, and platelet count. Clinical chemistry laboratory evaluations will include measures of blood urea nitrogen (BUN), creatinine, glucose, carbon dioxide, potassium, alanine transaminase (ALT), sodium, and chloride.

Hematology and chemistry laboratory results will be graded according to Table 6 and Table 7 respectively.

Table 6: Grading Scale for Clinical Hematology Parameters

Test	Normal	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (g/dL) (for screening purposes only)	M: LLN = 11.0 F: LLN = 10.5				
Hemoglobin, low		M: 10.0 to 10.9 F: 9.5 to 10.4	M: 9.0 to <10.0 F: 8.5 to <9.5	M: 7.0 to <9.0 F: 6.5 to <8.5	M: <7.0 F: <6.5
Eosinophils (cells/mm^3)	15-500	551-1,500	1,501-5,000	> 5,000	Hospitalization or ER Visit
Leukocytes (white blood cells) (cells/mm^3)	2,500 to 10,800				
Leukopenia		2,000 to 2,499	1,500 to 1,999	1,000 to 1,499	< 1,000
Leukocytosis		10,801-15,000	15,001-20,000	20,001-25,000	>25,000
Lymphocytes, low (cells/mm^3)	≥650	600 to <650	500 to <600	350 to <500	<350
Neutrophils, low (cells/mm^3)	>1,000	800 to 1,000	600 to 799	400 to 599	<400
Platelets decreased (cells/mm^3)	≥125,000	100,000 to <125,000	50,000 to <100,000	25,000 to <50,000	<25,000

Table 7: Grading Scale for Clinical Chemistry Parameters

Test	Normal	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN (elevation) (mg/dL)	7-25	26-28	29-31	> 31	Requires dialysis
Creatinine (elevation)[a] (mg/dL)	M: 0.7-1.4 F: 0.5-1.1	1.1-1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 to < 1.5 x baseline	> 1.8 to <3.5 x ULN OR Increase of 1.5 to < 2.0 x baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x baseline
Glucose, Random (mg/dL)	65 to115				
Hypoglycemia		55 to 64	40 to <55	30 to <40	<30
Hyperglycemia		116 to 160	>160 to 250	>250 to 500	>500

Test	Normal	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Potassium (mEq/L; *mmol/L*)	3.4 to 5.6				
Hypokalemia		3.0 to < 3.4	2.5 to <3.0	2.0 to <2.5	<2.0
Hyperkalemia		5.6 to <6.0	6.0 to <6.5	6.5 to <7.0	≥7.0
SGPT/ALT (elevation) (U/L)	M:9 to 46 F: 6 to 29	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10 x ULN	≥ 10x ULN
Sodium (mEq/L; *mmol/L*)	136 to145				
Hyponatremia		130 to <136	125 to <130	121 to <125	≤120
Hypernatremia		146 to <150	150 to <154	154 to <160	≥160

[a] Will be graded as the highest grade met by either criterion

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. General Analysis Specifications

3.1.1. Global Analysis Principles

The following general analysis principles will be applied unless otherwise specified:

Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. Confidence intervals for means will be calculated via Student's t distribution. Categorical variables will be summarized as counts and percentages (based on the non-missing sample size). Exact binomial confidence intervals for percentages will be calculated using Clopper-Pearson methodology.

All tables will be annotated with the total number of subjects relevant to that table.

3.1.2. Reporting Conventions

The mean, standard deviation, and median (if there is an even number of observations) will be reported to one decimal place greater than the original data. The minimum, maximum, and median (if there is an odd number of observations) will be reported to the same number of decimal places as the original data. Percentages will be reported to the nearest whole number; non-zero values < 1% will be presented as "< 1"; values greater than 99% but less than 100% will be presented as "> 99".

In general, all subject level data will be listed, sorted by subject ID, and when appropriate by visit number within subject. Missing values will be displayed as a dash (-) in subject listings.

3.1.3. Analysis Software and Other Technical Details

All statistical analyses will be performed using SAS Version 9.4 or above, or R Version 4.2 or above.

3.2. Outcome Adjudication Committee

An outcome adjudication committee will be used to judge if the diarrhea is attributable to ETEC and determine

if a subject meets the primary endpoint by considering individual data as described in the adjudication charter.

The committee will be comprised of at least 3 individuals, who are experts on diarrheal illness case identification and pathogen diagnosis. The committee will also include a statistician/data analyst who will participate in the adjudication meeting but will not have a voting role in deliberations.

Specific duties and responsibilities will be outlined by charter prior to the start of the in-patient period of the study.

3.3. Analysis Populations

The Full Analysis Set (FAS) includes all subjects who have been challenged with E24377A (regardless if the whole intended challenge dose was ingested or a subject vomited just after ingestion) and have available data. The Full Analysis Set will be included in analyses of all endpoints.

3.4. Subgroups, Interactions and Covariates

Subgroup analyses are not planned for this protocol.

3.5. Handling of Missing Data

All attempts will be made to collect all data per protocol. As missing data are expected to be minimal, no imputation will be performed for missing values. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated.

3.6. Multiple Comparisons/Multiplicity

No formal statistical testing is planned for this study.

4. SUMMARY OF STUDY CONDUCT AND PARTICIPANTS

4.1. Study Challenge

Each subject will receive a single administration of approximately 4 x 10^9 cfu of the ETEC strain E24377A (lot 0807) by mouth at baseline (Day 1).

A sodium bicarbonate buffer solution of 2 g/150 mL water will be prepared. Each subject will drink 120 mL of this sodium bicarbonate buffer (in order to neutralize gastric acidity) one minute prior to ingesting the challenge inoculum. Thereafter, subjects will drink the challenge inoculum (approximately 4 x10^9 cfu) dissolved in the remaining 30 mL of buffer.

A listing of study challenge administration by subject will be presented in Listing 1.

4.2. Screen Failures

Table 7 will present a summary of the reasons that subjects were screened but not enrolled.

4.3. Demographics and Other Baseline Characteristics

Descriptive statistics will be presented for demographic and baseline clinical data including biological sex, gender identity, ethnicity, race, age, height, weight, and body mass index (BMI) (Table 8 and Table 9). Individual subject listings will be presented for all demographic and baseline clinical data (Listing 2).

4.4. Disposition of Subjects

The disposition of subjects in the study will be tabulated in Table 10, including the total number of subjects who were screened, enrolled, received challenge, and completed study follow-up.

A flowchart showing the disposition of study subjects, adapted from the Consort Statement [1], will be included (10.1 Disposition of Subjects

Figure 1). This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed.

A listing of subjects who terminated early from study follow-up and the reason will be included in Listing 3.

4.5. Protocol Deviations (PD)

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and Institutional Review Board (IRB) and agreed to by the investigator. Protocol deviations will be classified as minor or major based on the impact on data quality and patient safety. The classification will be done by PI and site team in agreement with CRO and Sponsor.

A summary of subject-specific protocol deviations will be presented by the reason for the deviation and the deviation category for all subjects (Table 11). All subject-specific protocol deviations and non-subject specific protocol deviations will be listed in Listing 4 and Listing 5.

5. CLINICAL EVALUATION

5.1. Primary Endpoint

The number and percentage of subjects meeting the primary endpoint and unadjudicated primary endpoint will be presented with corresponding 95% CIs in Table 12. Individual data contributing to the primary endpoint, including stool grade, weight, and timing relative to inoculation, as well as adjudication committee decision, will be listed in Listing 6.

5.2. Diarrhea Incidence and Severity

Table 13 will display the number and percentage of subjects with diarrhea, with corresponding 95% CIs, by maximum severity and maximum stool grade throughout the 120-hour observation period.

Total number and weight of grade 3-5 stools passed during the 120-hour observation period, as well as maximum number and weight of grade 3-5 stools during a 24-hour window, will be summarized by mean, standard deviation, median, minimum, and maximum in Table 14.

5.3. Time to Event

Time to meeting the primary endpoint, defined as the number of hours from challenge to first instance of at least moderate diarrhea deemed attributable to ETEC according to an adjudication committee (see Section 2.5.4 for more details), time to meeting the unadjudicated primary endpoint, defined as the number of hours from challenge to first instance of at least moderate diarrhea without adjudicator input, and time to diarrhea onset, defined as the number of hours from challenge to first grade 3-5 stool of a subject's first diarrhea episode, will be estimated based on the survival function calculated via Kaplan-Meier methodology, with 95% CIs estimated via log-log transformation. Quartiles (minimum, 25th percentile, 50th percentile, 75th percentile, and maximum) of time to primary endpoint and time to diarrhea onset will be presented in Table 16. Kaplan-Meier survival curves displaying the estimated probability of meeting the primary endpoint and unadjudicated

primary endpoint and the timing of diarrhea onset with Hall-Wellner confidence bands will be presented in 14.2 Clinical Data

Figure 2, Figure 3, and Figure 4, respectively. Hall-Wellner confidence bands are displayed on the Kaplan-Meier curves rather than pointwise confidence intervals in order to preserve a simultaneous coverage probability of 0.95 across confidence intervals for all time points of the survival function.

These figures will be generated in SAS according to the following pseudocode:

```
proc lifetest data=tte_data
  plots=survival(cb=hw failure atrisk(outside));
  time Hours * Censor(1);
run;
```

5.4. ETEC Disease Severity Score

Summary statistics (mean, standard deviation, median, minimum, and maximum) of ETEC disease severity score will be presented by component sub-score and total score in Table 16. Individual data contributing to ETEC disease severity score will be listed in Listing 7.

5.5. Self-Assessment of ETEC Illness Impact on Daily Activity at Day 7

Number and percentage of subject responses on ADLs are presented in Table 17.

5.6. ETEC Illness Intervention

The number and percentage of subjects requiring intervention due to ETEC illness, including early antibiotic treatment and IV fluid administration, are presented with corresponding 95% CIs in Table 18.

5.7. Functional Bowel Disorder Survey

A listing of positive responses (i.e., responses other than “No,” “Never”, etc.) to the Functional Bowel Disorder Survey will be provided in Listing 8.

5.8. Qualitative Shedding of Challenge Strain

The number and percentage of subjects with positive and negative fecal culture results for shedding of the challenge strain are presented by study day in Table 19.

5.9. Analysis of Exploratory Microbiology Endpoints

Exploratory analyses are not in the scope of this analysis plan. Exploratory analyses will be planned separately from the primary and secondary analyses and will be reported separately from the Clinical Study Report.

6. IMMUNOGENICITY EVALUATION

6.1. Analysis of Exploratory Immunogenicity Endpoints

All immunogenicity endpoints are considered exploratory. Exploratory analyses are not in the scope of this analysis plan. Exploratory analyses will be presented separately from the primary and secondary analyses and will be reported separately from the Clinical Study Report.

7. SAFETY EVALUATION

7.1. Medical History

All current illnesses and relevant past or pre-existing medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 26.1 or higher.

Individual subject listings of all reported prior and concurrent medical conditions will be presented in Listing 9.

7.2. Prior and Concomitant Medications

Prior and concomitant medications will be coded to the Anatomical Therapeutic Chemical (ATC) classification system as defined by the WHO Drug Dictionary. Summaries of medications will be presented by ATC levels 1 and 2 for subjects in the Full Analysis Set (Table 20).

Individual subject listings will be presented for all prior and concomitant medications in Listing 10.

7.3. ETEC Disease-Specific Solicited Events

Number and percentage of subjects experiencing ETEC disease-specific solicited events are presented by symptom with 95% confidence intervals in Table 22, and by symptom and maximum severity in Table 23 and Figure 5. Number and percentage of subjects experiencing ETEC disease specific solicited events by Study Day are presented in Table 24.

7.4. Adverse Events, Serious Adverse Events and Other Significant 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 population size. All adverse events reported will be included in the summaries and analyses.

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

- Overall summary of adverse events (Table 21);
- Summary of unsolicited adverse events (Table 25);
- Summary of unsolicited AEs by severity and relationship to study product (Table 26);
- Summary of AEs leading to study withdrawals (Table 27)
- Listing of subjects with solicited events (Listing 11);
- Listing of unsolicited AEs (Listing 12);
- Listing of SAEs (Listing 13);
- Bar charts of frequency and incidence of related AEs (Figure 6, Figure 7);
- Bar charts of frequency and incidence of unsolicited AEs (Figure 8, Figure 9).

7.5. Clinical Laboratory Evaluations

Listings of abnormal laboratory results are presented in Listing 14.

7.6. Vital Signs

Oral temperature is presented by assessment, severity and study day (Table 28). Individual subject listings of vital signs are presented in Listing 15.

7.7. Physical Evaluations

A complete physical examination [head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, lymph nodes, neurological, and musculoskeletal systems] will be performed during screening and on

admission. During in-patient period, a focused physical exam will be conducted daily.

Physical evaluation findings are listed in Listing 16.

7.8. Pregnancies

Subjects will be screened by pregnancy test before participation in this study and instructed to use effective contraception. Sexually active people of childbearing potential will have to use birth control. Abstinence from sexual intercourse that could result in pregnancy is acceptable.

Pregnancies will be captured through Day 29. Pregnancy will be followed for outcome, and outcome will be reported (e.g., any premature terminations, elective or therapeutic, and any spontaneous abortions or stillbirths, as well as the health status of the mother and child including date of delivery and infant's gender, length and weight).

Individual pregnancy test results are listed in Listing 17. Any pregnancies reported during the study will be recorded in Listing 18.

8. INTERIM ANALYSIS AND DATA REVIEWS

8.1. Interim Analyses

Following a partial lock of challenge outcome data, subject-level data listings and figures will be generated according to an adjudication charter. The adjudication committee will convene to review these data listings and figures and determine which subject has met the primary endpoint. After adjudicated primary endpoint determinations are complete, topline results will be generated. Topline results will include summaries of the primary endpoint, demographics, and stool output data. Tables and listings to be included in the topline report are marked with an asterisk (*). Although topline results will be generated while subject follow-up is ongoing, these results will be considered final as they will be generated using clean and complete data.

9. REFERENCES

1. Drummond R. CONSORT Revised: Improving the Reporting of Randomized Clinical Trials. JAMA. 2001; 285(15):2006-2007.

APPENDIX A: TABLE MOCK-UPS

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14.1 Description of Study Subjects

14.1.1 Screen Failures

Table 7: Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
All Screened Subjects (N=X)	Total number of subjects who failed any eligibility criterion or were eligible but not enrolled	x	xx
Subjects who failed to meet Inclusion Criteria (N=X)	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Subjects who met Exclusion Criteria (N=X)	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Subjects who were Eligible but Not Enrolled (N=X)	Alternate subject	x	xx
	Time commitment	x	xx
	Concern of potential risks	x	xx
	Number of procedures/blood draws	x	xx
	Unable to contact subject	x	xx
	COVID-19 pandemic	x	xx
	Other	x	xx

Note: N = Number of subjects belonging to the corresponding inclusion/exclusion category; n = Number of subjects who met the corresponding inclusion/exclusion criterion.
[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of subjects in the corresponding category (N).

14.1.2 Demographic Data

Table 8: Summary of Categorical Demographic and Baseline Characteristics - All Enrolled Subjects*

Variable	Characteristic	All Subjects (N=X)	
		n	%
Sex	Male	x	xx
	Female		
	Intersex		
	Not Reported		
Gender	Cisgender Man	x	xx
	Cisgender Woman		
	Genderqueer		
	Gender Non-binary		
	Gender Non-conforming		
	Transgender Man/ Trans Man		
	Transgender Woman/ Trans Woman		
	Other		
	Not Reported		
Ethnicity	Not Hispanic or Latino	x	xx
	Hispanic or Latino		
	Not Reported		
	Unknown		
Race	American Indian or Alaska Native	x	xx
	Asian		
	Native Hawaiian or Other Pacific Islander		
	Black or African American		
	White		
	Multi-Racial		
	Unknown		
	Not Reported		

Note: N = Number of enrolled subjects; n = Number of enrolled subjects who identify with the corresponding demographic information.

Table 9: Summary of Continuous Demographic and Baseline Characteristics - All Enrolled Subjects*

Variable	Statistic	All Subjects (N=X)
Age (years)	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Height (cm)	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Weight (kg)	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
BMI (kg/m^2)	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Note: N = Number of enrolled subjects.		

14.1.3 Disposition of Subjects

Table 10: Subject Disposition - All Enrolled Subjects

Subject Disposition	All Subjects (N=X)	
	n	%
Screened	x	--
Enrolled	x	100
Received Challenge	x	xx
Completed Inpatient Period Per Protocol	x	xx
Completed Outpatient Visit (Study Day 29)	x	xx
Completed Follow-up (Study Day 180) [a]	x	xx
Terminated Early from Study	x	xx

Note: N = Number of enrolled subjects; n = Number of subjects who completed the corresponding study milestone.

[a] For additional details about subjects who terminated early, refer to Listing 2.

14.1.4 Protocol Deviations

Table 11: Distribution of Subject-Specific Protocol Deviations by Category and Type - All Enrolled Subjects

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

Category	Deviation Type	All Subjects (N=X)	
		No. of Subjects	No. of Deviations
	Other	x	x
Treatment administration	Any type	x	x
	Required procedure done incorrectly	x	x
	Study product temperature excursion	x	x
	Other	x	x
Note: N = Number of enrolled subjects.			

14.2 Clinical Data

Table 12: Number and Percentage of Subjects Meeting the Primary Endpoint and Unadjudicated Primary Endpoint - Full Analysis Set*

Endpoint Type	All Subjects (N=X)		
	n	%	95% CI [a]
Primary Endpoint	x	xx	xx.x, xx.x
Unadjudicated Primary Endpoint	x	xx	xx.x, xx.x
Notes: N = Number of subjects in the Full Analysis Set; n = Number of subjects meeting the corresponding endpoint. [a] Exact binomial confidence interval calculated via Clopper-Pearson methodology.			

Table 13: Maximum Diarrhea Severity - Full Analysis Set*

Variable	Category	All Subjects (N=X)		
		n	%	95% CI [b]
Maximum Diarrhea Severity [a]	None	x	xx	-
	Mild	x	xx	-
	Moderate	x	xx	-
	Severe	x	xx	xx.x, xx.x
	Any Diarrhea (Mild-Severe)	x	xx	xx.x, xx.x

Notes: N = Number of subjects in the Full Analysis Set; n = Number of subjects with the corresponding maximum diarrhea severity during the inpatient period.

[a] Maximum diarrhea severity refers to the maximum severity of any diarrhea episode passed by each subject during the inpatient period.

[b] Exact binomial confidence interval calculated via Clopper-Pearson methodology.

Table 14: Summaries of Number and Weight of Grade 3-5 Stools - Full Analysis Set*

Variable	Statistic	All Subjects (N=X)
Total Number of Grade 3-5 Stools during 120-Hour Observation Period	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Total Number of Grade 3-5 Stools during Inpatient Period	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Total Weight (g) of Grade 3-5 Stools during 120-Hour Observation Period	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Total Weight (g) of Grade 3-5 Stools during Inpatient Period	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Maximum Number of Grade 3-5 Stools in 24-Hour Window during 120-Hour Observation Period	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Maximum Number of Grade 3-5 Stools in 24-Hour Window during Inpatient Period	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx

Variable	Statistic	All Subjects (N=X)
Maximum Weight (g) of Grade 3-5 Stools in 24-Hour Window during 120-Hour Observation Period	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Maximum Weight (g) of Grade 3-5 Stools in 24-Hour Window during Inpatient Period	Mean	xx.x
	Standard Deviation	xx.x
	Median	xx.x
	Minimum	xx
	Maximum	xx
Note: N = Number of subjects in the Full Analysis Set.		

Table 15: Time to Primary Endpoint, Unadjudicated Primary Endpoint, and Diarrhea Onset - Full Analysis Set*

Event	Statistic	All Subjects (N=X)	
		Estimated Time to Event (hours) [e]	95% CI [f]
Primary Endpoint [a]	Minimum	xx	xx.x, xx.x
	25th Percentile	xx	xx.x, xx.x
	50th Percentile (Median)	xx	xx.x, xx.x
	75th Percentile	xx	xx.x, xx.x
	Maximum	xx	xx.x, xx.x
Primary Endpoint (Sensitivity Analysis) [b]	Minimum	xx	xx.x, xx.x
	25th Percentile	xx	xx.x, xx.x
	50th Percentile (Median)	xx	xx.x, xx.x
	75th Percentile	xx	xx.x, xx.x
	Maximum	xx	xx.x, xx.x
Unadjudicated Primary Endpoint [c]	Minimum	xx	xx.x, xx.x
	25th Percentile	xx	xx.x, xx.x
	50th Percentile (Median)	xx	xx.x, xx.x
	75th Percentile	xx	xx.x, xx.x
	Maximum	xx	xx.x, xx.x
Diarrhea Onset [d]	Minimum	xx	xx.x, xx.x
	25th Percentile	xx	xx.x, xx.x
	50th Percentile (Median)	xx	xx.x, xx.x
	75th Percentile	xx	xx.x, xx.x
	Maximum	xx	xx.x, xx.x

Notes: N = Number of subjects in the Full Analysis Set.

[a] Time to primary endpoint is defined as the number of hours from challenge to first grade 3-5 stool that meets at least moderate severity criteria, occurs within a diarrhea episode that began prior to 120 hours post challenge, and is deemed attributable to ETEC by an adjudication committee. Subjects who met the primary endpoint according to the adjudication committee but whose stools did not meet the frequency or weight thresholds for moderate or severe diarrhea will be considered to have met the primary endpoint at time of antibiotic administration.

[b] Time to primary endpoint for the sensitivity analysis is defined as the number of hours from challenge to first grade 3-5 stool that meets at least moderate severity criteria, occurs within a diarrhea episode that began prior to 120 hours post challenge, and is deemed attributable to ETEC by an adjudication committee. Subjects who met the primary endpoint according to the adjudication committee but whose stools did not meet the frequency or weight thresholds for moderate or severe diarrhea will be considered to have met the primary endpoint at 120 hours post challenge.

[c] Time to unadjudicated primary endpoint is defined as the number of hours between challenge and the first grade 3-5 stool that passes the frequency or weight threshold of moderate diarrhea and occurs within a diarrhea episode that began prior to 120 hours post challenge.

[d] Time to diarrhea onset is defined as the number of hours from challenge to first grade 3-5 stool of a subject's first diarrhea episode during the inpatient period.

[e] Estimated time to event is based on the survival function calculated via Kaplan-Meier methodology. Subjects who did not meet the primary endpoint will be right censored at 120 hours post-challenge or time of discharge from the inpatient unit, whichever is first. Subjects who experienced no diarrhea episodes during the inpatient period will be right censored at the time of discharge from the inpatient unit.

[f] Confidence intervals are calculated via log-log transformation.

Table 16: Summaries of ETEC Disease Severity Score - Full Analysis Set

Score Component	Component Definition	Score [a]	All Subjects (N=X)
			n (%)
Objective Signs Sub-Score	Vomiting frequency and fever	0	x (xx)
		1	
		2	
Subjective Symptoms Sub-Score	Lightheadedness, nausea, malaise, headache, and abdominal cramps.	0	
		1	
		2	
Stool Output Sub-Score	Diarrhea frequency and volume	0	
		1	
		2	
		3	
		4	
Total Score	Sum of all score components	0	
		1	
		2	
		3	
		4	
		5	
		6	
		7	
		8	

Notes: N = Number of subjects in the Full Analysis Set; n = Number of subjects with the corresponding score for each ETEC disease severity score component.
[a] Higher scores correspond to more severe ETEC disease.

Table 17: ETEC Impact on ADLs - Full Analysis Set

ADL Question		All Subjects (N=X)		
	Response	n	%	95% CI[a]
If traveling for vacation or business, would you have changed your itinerary?	Yes	x	xx	xx.x, xx.x
	No			
Would you have stayed in bed?	Yes			
	No			

Notes: N = Number of subjects in the Full Analysis Set; n = Number of subjects providing the corresponding response to each question; ADL = Activity of Daily Living.

[a] Exact binomial confidence interval calculated via Clopper-Pearson methodology.

Table 18: ETEC Illness Interventions - Full Analysis Set

Intervention	All Subjects (N=X)		
	n	%	95% CI[a]
Early antibiotic treatment (prior to Day 6)	x	xx	xx.x, xx.x
Administration of IV fluids	x	xx	xx.x, xx.x

Notes: N = Number of subjects in the Full Analysis Set; n = Number of subjects who received the corresponding intervention due to ETEC illness.
[a] Exact binomial confidence interval calculated via Clopper-Pearson methodology.

Table 19: Qualitative Shedding of the E24377A Challenge Strain by Study Day - Full Analysis Set

Study Day	Antibiotic Treatment Status[b]	N	Fecal Culture Result[a]			
			Positive		Negative	
			n	%	n	%
Any Day	Any Status	xx	xx	xx	xx	xx
	Treated					
	Not Treated					
Day 1	Any Status					
	Treated					
	Not Treated					
Day 2	Any Status					
	Treated					
	Not Treated					
Day 3	Any Status					
	Treated					
	Not Treated					
Day 4	Any Status					
	Treated					
	Not Treated					
Day 5	Any Status					
	Treated					
	Not Treated					
Day 6	Any Status					
	Treated					
	Not Treated					
Day 7	Any Status					
	Treated					
	Not Treated					
Day 8	Any Status					
	Treated					
	Not Treated					
Day 9	Any Status					
	Treated					
	Not Treated					

N = Number of subjects with a fecal culture result on the given study day with the corresponding antibiotic treatment

status on that day; n = Number of subjects with the corresponding fecal result and antibiotic treatment status on the given study day.

[a] Only one fecal culture result is counted per subject per day. If a subject has both positive and negative culture results from fecal samples collected on the same day, then the positive result is counted.

[b] A subject is considered treated if they received at least one dose of antibiotics prior to sample collection for the reported result. If at least one positive culture result was reported on a given study day, then the antibiotic treatment status prior to the last positive result on that day is reported. If only negative culture results were reported on a given study day, then the antibiotic treatment status prior to the last negative result on that day is reported.

14.4 Concomitant Medications

Table 20: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification - Full Analysis Set

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

Note: N = Number of subjects in the Full Analysis Set; n = Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 21: Overall Summary of Adverse Events - Full Analysis Set

		All Subjects (N=X)	
Event Category[a]	**Subcategory[a]**	**n**	**%**
At least one ETEC disease-specific solicited event	Any Severity	x	x
	Mild (Grade 1)		
	Moderate (Grade 2)		
	Severe (Grade 3)		
	Potentially Life-Threatening (Grade 4)		
At least one unsolicited adverse event	--		
At least one unsolicited adverse event related to challenge	Any Severity		
	Mild (Grade 1)		
	Moderate (Grade 2)		
	Severe (Grade 3)		
	Potentially Life-Threatening (Grade 4)		
At least one unsolicited adverse event related to study procedure	Any Severity		
	Mild (Grade 1)		
	Moderate (Grade 2)		
	Severe (Grade 3)		
	Potentially Life-Threatening (Grade 4)		
At least one unsolicited adverse event related to antibiotics	Any Severity		
	Mild (Grade 1)		
	Moderate (Grade 2)		
	Severe (Grade 3)		
	Potentially Life-Threatening (Grade 4)		
At least one severe (Grade 3) unsolicited adverse event	Any Relationship to Challenge		
	Related to Challenge		
	Not Related to Challenge		
At least one serious adverse event[b]	--		
At least one serious adverse reaction[b]	--		
At least one suspected unexpected serious adverse reaction	--		

		All Subjects (N=X)	
Event Category[a]	**Subcategory[a]**	**n**	**%**
At least one adverse event leading to early termination[c]	--		
At least one new chronic illness	--		
At least one adverse event of special interest[d]	--		

Notes: N = Number of subjects in the Full Analysis Set; n = Number of subjects with the corresponding event.
[a] Subjects are counted once for each subcategory regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Section 9.3.6.
[c] As reported on the Adverse Event eCRF.
[d] Adverse events of special interest (AESIs) may include the development of Irritable Bowel Syndrome or other continuing gastrointestinal condition.

14.3.1.1 Solicited Adverse Events

Table 22: Number and Percentage of Subjects Experiencing ETEC Disease-Specific Solicited Events with 95% Confidence Intervals by Symptom - Full Analysis Set

Sign or Symptom	All Subjects (N=X)		
	n	%	95% CI [a]
Any Sign or Symptom	x	xx	x.x, x.x
Malaise			
Loss of Appetite			
Headache			
Chills			
Nausea			
Abdominal Pain			
Abdominal Cramps			
Myalgia			
Arthralgia			
Urgency of Defecation			
Lightheadedness			
Diarrhea			
Hypovolemia			
Fever			
Vomiting			

Notes: N = Number of subjects in the Full Analysis Set; n = Number of subjects reporting the corresponding sign or symptom.
[a] Exact binomial confidence interval calculated using Clopper-Pearson methodology.

Table 23: Number and Percentage of Subjects Experiencing ETEC Disease Specific Solicited Events by Symptom and Maximum Severity - Full Analysis Set

Sign or Symptom	Severity	All Subjects (N=X)	
		n	%
Any Sign or Symptom	None	x	xx
	Mild	x	xx
	Moderate	x	xx
	Severe	x	xx
	Potentially Life-Threatening	x	xx
Malaise	None		
	Mild		
	Moderate		
	Severe		
	Potentially Life-Threatening		
Loss of Appetite	None		
	Mild		
	Moderate		
	Severe		
	Potentially Life-Threatening		
[Continue with remaining solicited symptoms…]	None		
	Mild		
	Moderate		
	Severe		
	Potentially Life-Threatening		
Notes: N = Number of subjects in the Full Analysis Set. n = Number of subjects with reported event. Severity is the maximum severity reported over all solicited symptoms post challenge for each subject.			

Table 24: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity and Days - Full Analysis Set

Sign or Symptom	Severity	Day 1 (N=X)		Day 2 (N=X)		Day 3 (N=X)		Day 4 (N=X)		Day 5 (N=X)		Day 6 (N=X)		Day 7 (N=X)		Day 8 (N=X)		Day 9 (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Sign or Symptom	None																		
	Mild																		
	Moderate																		
	Severe																		
	Potentially Life-Threatening																		
	Not Reported																		
Malaise	None																		
	Mild																		
	Moderate																		
	Severe																		
	Potentially Life-Threatening																		
	Not Reported																		
Loss of Appetite	None																		
	Mild																		
	Moderate																		
	Severe																		
	Potentially Life-Threatening																		
	Not Reported																		
[Continue with remaining solicited symptoms…]	None																		
	Mild																		
	Moderate																		
	Severe																		
	Potentially Life-Threatening																		
	Not Reported																		

Notes: N = Number of subjects in the Full Analysis Set; n = Number of subjects with reported event.
Severity is the maximum severity reported post challenge for each subject on each day.

14.3.1.2 Unsolicited Adverse Events

Table 25: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term - Full Analysis Set

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

Note: N = Number of subjects in the Full Analysis Set; n = Number of subjects with reported event; Events = Total frequency of events reported.

Table 26: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, and Relationship to Challenge - Full Analysis Set

MedDRA System Organ Class	MedDRA Preferred Term	Severity	All Subjects (N = X)								
			Related to Challenge			Not Related to Challenge			All Events		
			n	%	Events	n	%	Events	n	%	Events
Any SOC	Any PT	Any Severity	x	xx	x	x	xx	x	x	xx	x
		Mild	x	xx	x	x	xx	x	x	xx	x
		Moderate	x	xx	x	x	xx	x	x	xx	x
		Severe	x	xx	x	x	xx	x	x	xx	x
		Potentially Life-Threatening	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	[PT 1]	Any Severity	x	xx	x	x	xx	x	x	xx	x
		Mild	x	xx	x	x	xx	x	x	xx	x
		Moderate	x	xx	x	x	xx	x	x	xx	x
		Severe	x	xx	x	x	xx	x	x	xx	x
		Potentially Life-Threatening	x	xx	x	x	xx	x	x	xx	x
	[PT 2]	Any Severity	x	xx	x	x	xx	x	x	xx	x
		Mild	x	xx	x	x	xx	x	x	xx	x
		Moderate	x	xx	x	x	xx	x	x	xx	x
		Severe	x	xx	x	x	xx	x	x	xx	x
		Potentially Life-Threatening	x	xx	x	x	xx	x	x	xx	x
…	…										

Note: N = Number of subjects in the Full Analysis Set; n = Number of subjects reporting adverse events of the corresponding SOC, PT, maximum severity, and relationship to challenge.

Table 27: Summary of Adverse Events Leading to Study Withdrawal by MedDRA System Organ Class and Preferred Term - Full Analysis Set

MedDRA System Organ Class	MedDRA Preferred Term	All Subjects (N=X)	
		n	%
Any SOC	Any PT	x	xx
[SOC 1]	Any PT		
	[PT 1]		
	[PT 2]		
[SOC 2]	Any PT		
	[PT 1]		
	[PT 2]		
…	…		
Note: N = Number of subjects in the Full Analysis Set; n = Number of subjects with reported event.			

14.3.2 Displays of Vital Signs

Table 28: Oral Temperature by Maximum Severity and Study Day - Full Analysis Set

Study Day	N	Normal		Mild		Moderate		Severe		Potentially Life-Threatening	
		n	%	n	%	n	%	n	%	n	%
Baseline (Day -1)	x	x	xx	x	xx	x	xx	x	xx	x	xx
Day 1 (30 minutes after challenge)											
Day 2											
Day 3											
Day 4											
Day 5											
Day 6											
Day 7											
Day 8											
Day 9											
Day 29											
Max Severity Post Baseline											

Notes: N = Number of subjects in the Full Analysis Set with available data at the corresponding time point; N is the denominator for percentages; n = Number of subjects with maximum oral temperature of the corresponding severity on the given study day.

The “Max Severity Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. If a subject has only ungraded results post baseline, their maximum severity is considered “None”.

APPENDIX B: FIGURE MOCK-UPS

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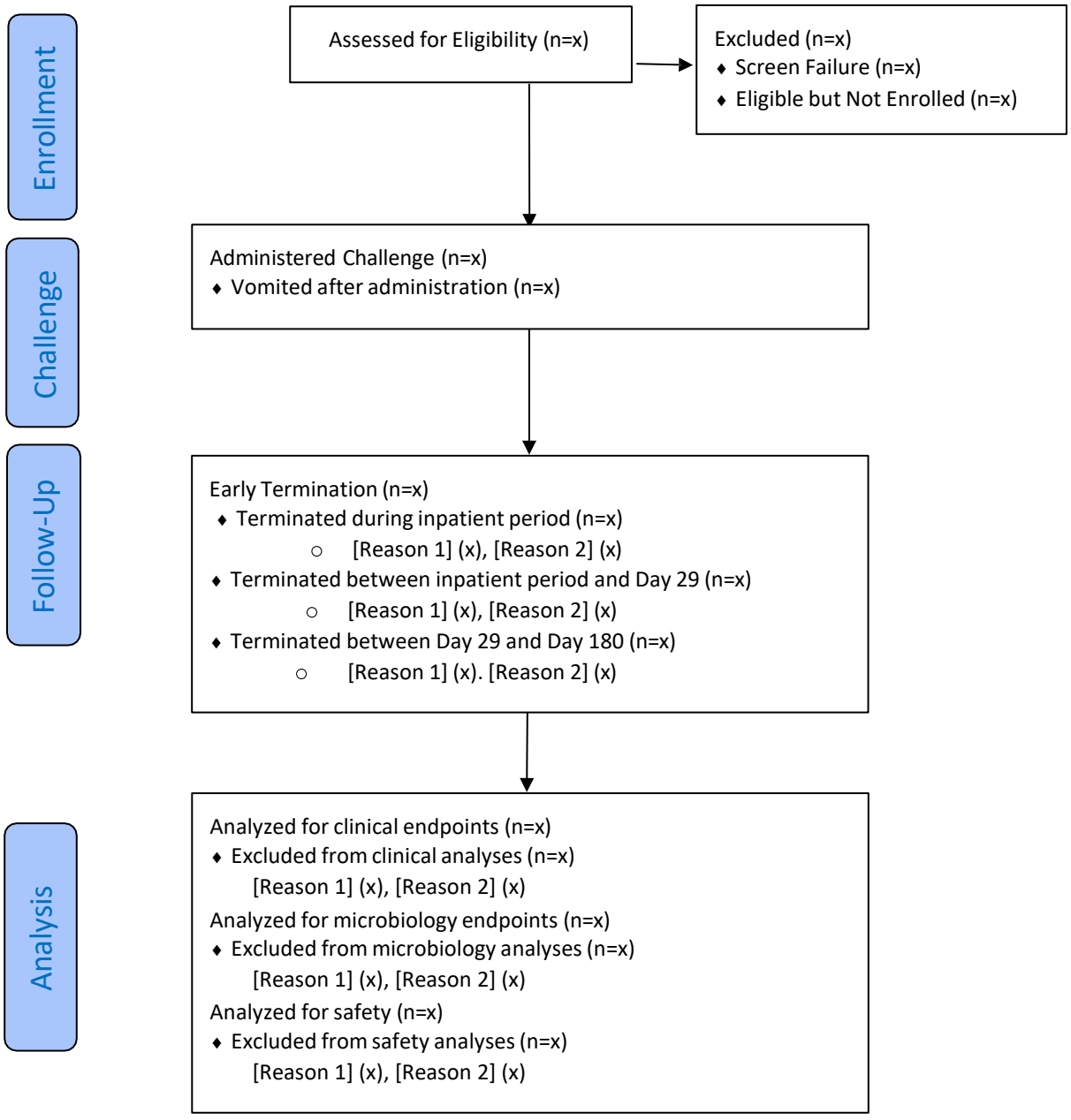
10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram



14.2 Clinical Data

Figure 2: Time to Primary Endpoint and Unadjudicated Primary Endpoint - Full Analysis Set

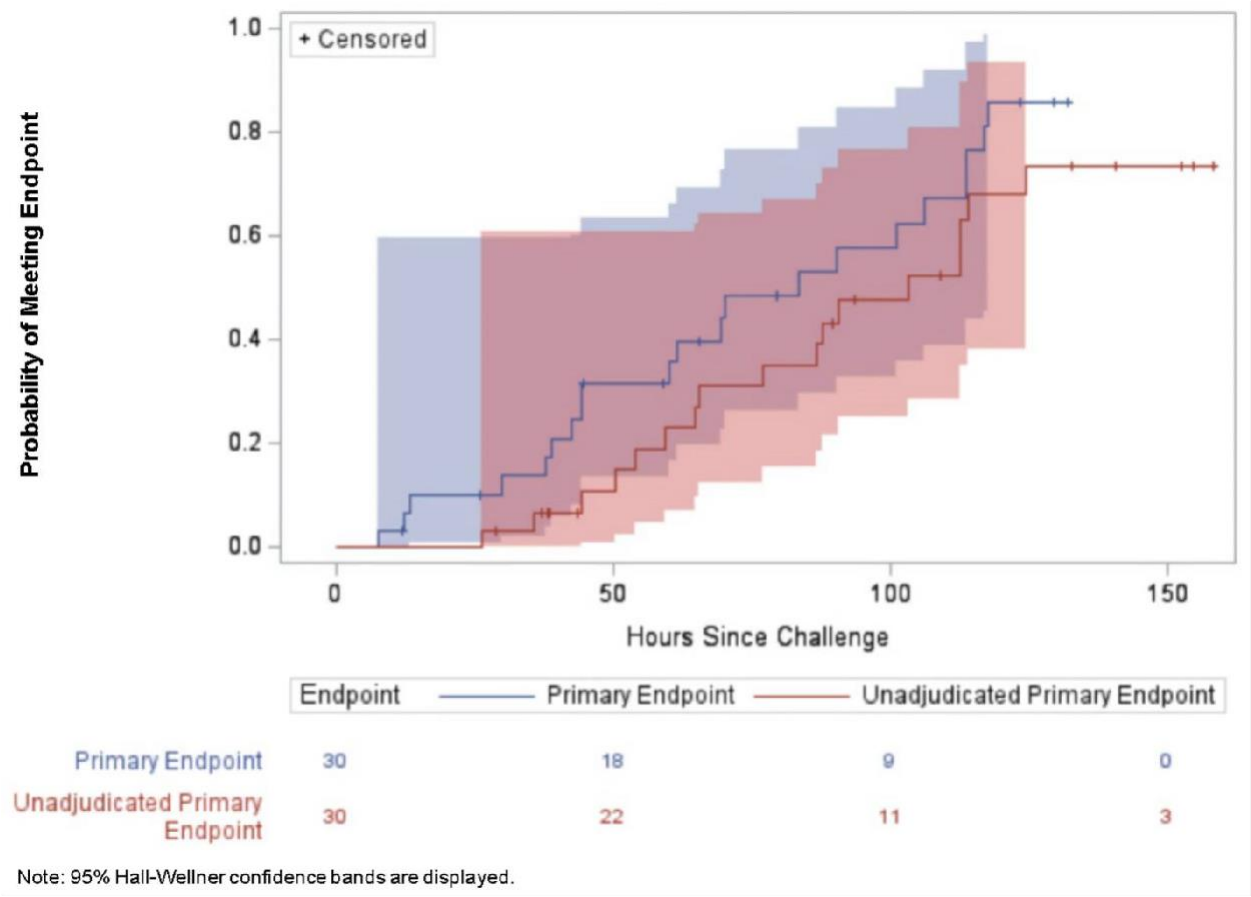


Figure with similar format:

Figure 3: Time to Primary Endpoint Sensitivity Analysis - Full Analysis Set

[Implementation Note: This figure will display only one curve for time to primary endpoint, with subjects who met the primary endpoint but did not meet the stool frequency and weight criteria having event time imputed as 120 hours post challenge.]

Figure 4: Time to Diarrhea Onset - Full Analysis Set

[Implementation Note: This figure will display only one curve for diarrhea onset.]

14.3 Safety Data

Figure 5: Maximum Severity of ETEC Diseases-Specific Solicited Events by Sign or Symptom - Full Analysis Set

[Implementation Note: A generic sample figure is shown below. The bar chart should be presented in a single-paneled figure labeled as "All Subjects (N=X)", where N = the number of subjects in the Full Analysis Set. Axes should be labeled as follows: y-axis label: Sign or Symptom, x-axis label: Percentage of Subjects (%). Subjects are counted at most once per sign or symptom at the maximum severity reported.]

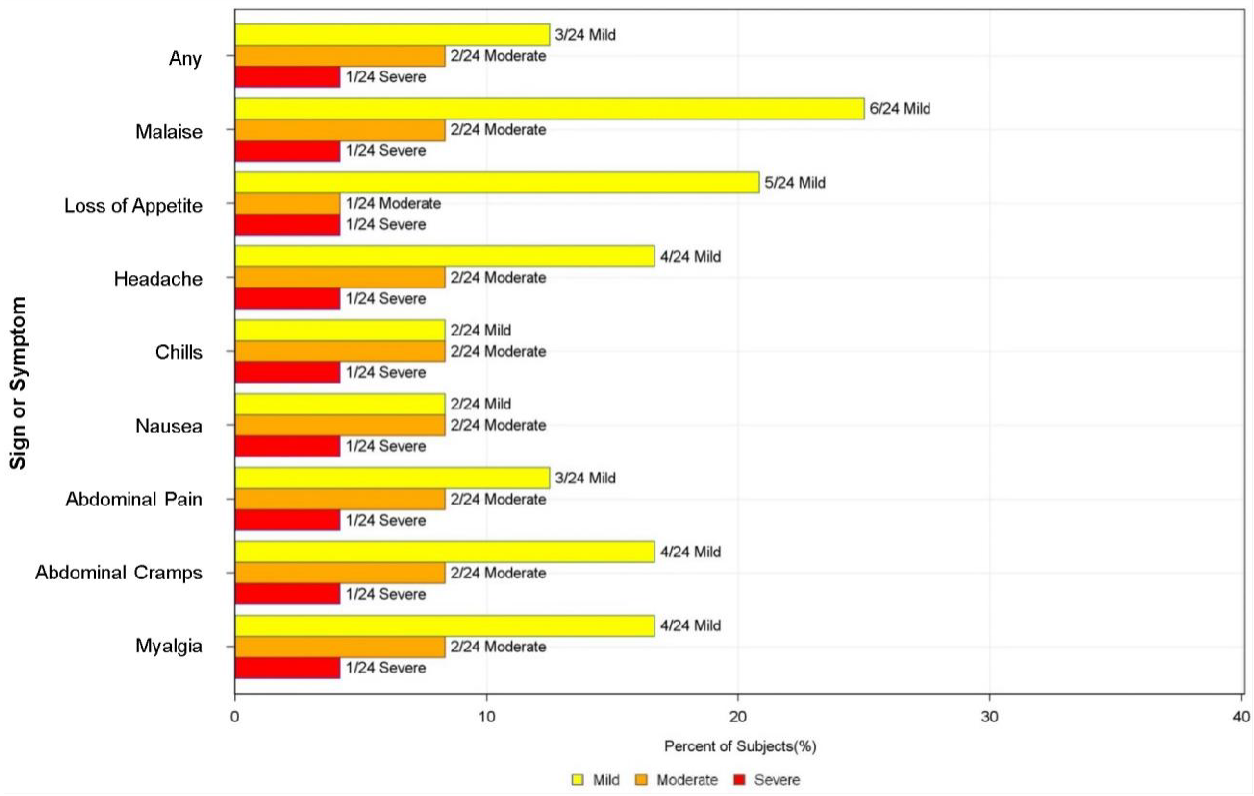


Figure 6: Number of Unsolicited Adverse Events by MedDRA System Organ Class and Severity - Full Analysis Set

[Implementation Note: A generic sample figure is shown below. The figure can be shaded with the default coloring instead of the patterns. The bar chart should be presented in a single-paneled figure labeled as "All Subjects (N=X)", where N = the number of subjects in the Full Analysis Set. Axes should be labeled as follows: y-axis label: System Organ Class, x-axis label: Number of Events.]

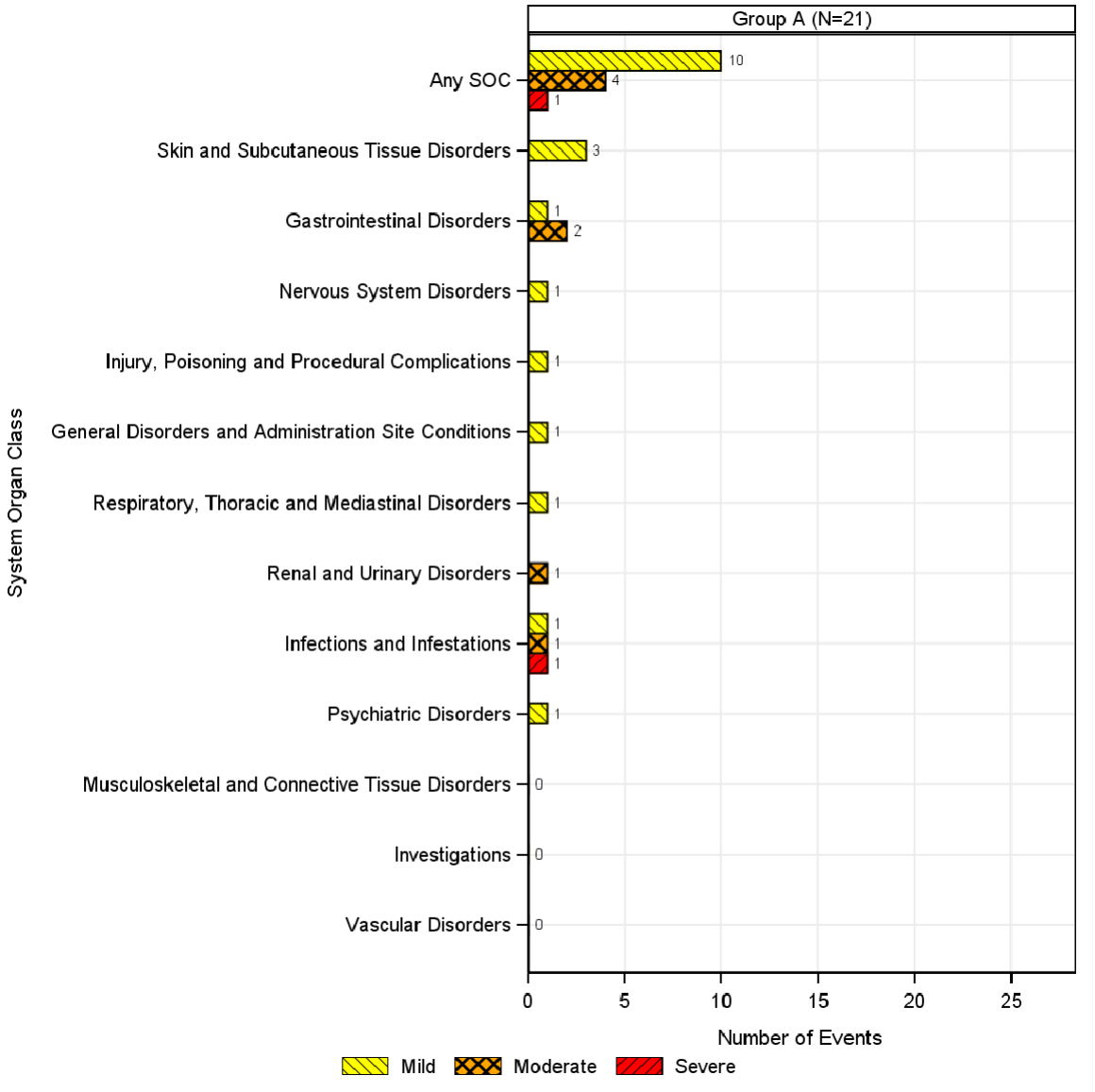


Figure 7: Percentage of Subjects Reporting Unsolicited Adverse Events by MedDRA® System Organ Class and Maximum Severity - Full Analysis Set

[Implementation Note: A generic sample figure is shown below. The figure can be shaded with the default coloring instead of the patterns. The bar chart should be presented in a single-paneled figure labeled as "All Subjects (N=X)", where N = the number of subjects in the Full Analysis Set. Axes should be labeled as follows: y-axis label: System Organ Class, x-axis label: Percent of Subjects (%). Subjects are counted at most once at the maximum severity across for any events in the applicable SOC.]

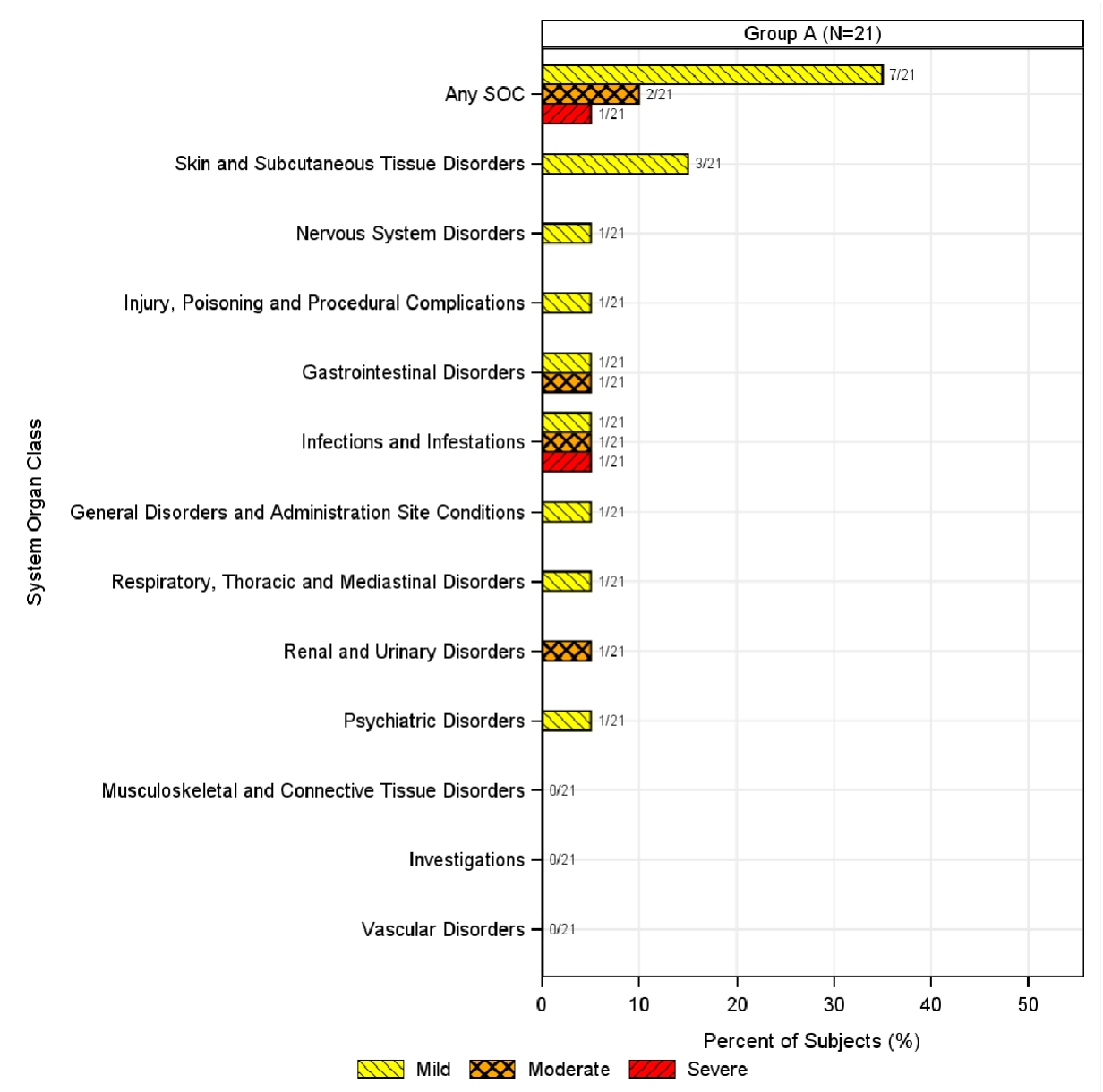


Figure 8: Number of Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Challenge - Full Analysis Set

[This figure will be similar to Figure 6. Bars will be categorized by relationship to challenge instead of severity.]

Figure 9: Percentage of Subjects Reporting Unsolicited Adverse Events by MedDRA System Organ Class and Maximum Relationship to Challenge - Full Analysis Set

[This figure will be similar to Figure 7. Bars will be categorized by relationship to challenge instead of severity.]

APPENDIX C: LISTING MOCK-UPS

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16.2.5 Compliance and/or Drug Concentration Data

Listing 1: Study Challenge Administration*

Subject ID	Was Challenge Administered?	Date of Challenge Administration	Time of Challenge Administration	Did Subject Vomit after Challenge Administration?
XXXXXXX	Yes / No	DDMMYYYY	xx:xx	Yes / No / N/A

16.2.4.1 Demographic Data

Listing 2: Demographic Data

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

Subject ID	Sex	Age at Screening (years)	Ethnicity	Race	Height (cm)	Weight (kg)	BMI (kg/m^2)

16.2.1 Discontinued Subjects

Listing 3: Early Terminations

[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.]

Subject ID	Category	Reason for Early Termination	Study Day

16.2.2.1 Subject-Specific Protocol Deviations

Listing 4: 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."]

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

16.2.2.2 Non-Subject Specific Protocol Deviations

Listing 5: 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 by Start Date.]

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

16.2.6 Individual Clinical Data

16.2.6.1 Grade 3-5 Stool Output

Listing 6: Grade 3-5 Stool Output*

[Implementation Note: The text in blue shows an example entry. Actual data should be presented in black text.]

Subject ID	Diarrhea Episode [a] No.	Grade 3-5 Stool No.	Time of Grade 3-5 Stool Relative to Challenge	Stool Weight	Stool Grade	Grade 3-5 Stools Passed within Previous 24 Hours	Total Number of Grade 3-5 Stools within Previous 24 Hours	Total Weight of Grade 3-5 Stools within Previous 24 Hours	Did Episode Meet Frequency and/or Weight Threshold for Primary Endpoint?	Did Episode Begin Prior to 120 Hours Post Challenge?	Did Subject Meet Unadjudicated Primary Endpoint? [b]	Did Subject Meet Primary Endpoint? [c]	Qualifying Information Provided by Adjudication Committee
xxxxx	1	1	13 hrs, 2 min	105 g	5	Stool 1	1	105 g	Yes	Yes	Yes	Yes	-
		2	16 hrs, 14 min	232 g	5	Stools 1-2	2	337 g					
		3	29 hrs, 45 min	107 g	3	Stools 1-3	3	444 g					
		4	42 hrs, 29 min	52 g	2	Stools 3-4	2	159 g					
	2	1	105 hrs, 55 min	32 g	3	Stool 1	1	32 g	No	Yes			
		2	122 hrs, 3 min	30 g	3	Stools 1-2	2	62 g					

Notes: Yellow highlighted cells indicate that the stool frequency or weight threshold for the primary endpoint has been met.

[a] A diarrhea episode starts when the first grade 3-5 stool that contributes to diarrhea of any severity is passed. A diarrhea episode ends when a subject has not passed any grade 3-5 stools within the past 24 hours.

[b] Moderate to severe diarrhea is defined as having a moderate and/or severe diarrhea episode beginning prior to 120 hours after challenge.

[c] The primary endpoint is defined as having a moderate and/or severe diarrhea episode or ETEC symptoms beginning prior to 120 hours after challenge, deemed attributable to ETEC as decided by an adjudication committee of experts in diarrheal illness.

16.2.6.2 Individual Data Contributing to ETEC Disease Severity Score

Listing 7: Individual Data Contributing to ETEC Disease Severity Score

Subject ID	Maximum # of Vomiting Episodes in 24-Hour Window	Fever?	Lightheaded-ness? (Severity)	Nausea? (Severity)	Malaise? (Severity)	Headache? (Severity)	Abdominal Cramps? (Severity)	Maximum # of Grade 3-5 Stools in 24-Hour Window	Maximum Weight of Grade 3-5 Stools in 24-Hour Window	ETEC Disease Severity Score
xxxxx	x	Yes/No	Yes/No (Severity)	Yes/No (Severity)	Yes/No (Severity)	Yes/No (Severity)	Yes/No (Severity)	x	xxx g	x

16.2.6.3 Functional Bowel Disorder Survey

Listing 8: Positive Responses to Functional Bowel Disorder Survey

[Implementation Note: List only questions with at least one "positive" response, i.e. a response other than "No," "Never," etc. If a subject has a positive response at only one visit (screening or Day 180), still list the subject's response at both visits.]

Subject ID	Question Category	Question	Response at Screening	Response at Day 180
xxxxx	Symptoms in the Esophagus / Symptoms of the Stomach and Intestines / Other	[Question 1]	Never / Less than one day a month / one day a month / Yes / No / etc.	Never / Less than one day a month / one day a month / Yes / No / etc.
xxxxx	Symptoms in the Esophagus / Symptoms of the Stomach and Intestines / Other	[Question 2]	Never / Less than one day a month / one day a month / Yes / No / etc.	Never / Less than one day a month / one day a month / Yes / No / etc.
xxxxx	Symptoms in the Esophagus / Symptoms of the Stomach and Intestines / Other	Continue with additional questions…	Never / Less than one day a month / one day a month / Yes / No / etc.	Never / Less than one day a month / one day a month / Yes / No / etc.

16.2.4.2 Medical History

Listing 9: Medical History

[Implementation Note: "Condition Start Day" and "Condition End Day" are relative to enrollment (which is Day 1, day before enrollment is Day -1).]

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

16.2.9.1 Prior and Concomitant Medications

Listing 10: Prior and Concomitant Medications

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

16.2.7.1 Solicited Events

Listing 11: ETEC Disease-Specific Solicited Events

Subject ID	Study Day	Assessment Type	Symptom	Severity
		Subjective/Objective		
Notes: Only ETEC disease-specific solicited events that are deemed related to challenge are listed.				

16.2.7.2 Unsolicited Adverse Events

Listing 12: Unsolicited Adverse Events

Adverse Event	No. of Days Post Associated Dose (Duration)	Severity	SAE?	Relationship to Challenge	Relationship to study procedure	Relationship to Antibiotics	If not related to challenge, antibiotics, or study procedure, Alternative Etiology	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , AE Number: , AESI?:											
Comments:											
Subject ID: , AE Number: , AESI?:											
Comments:											
Note: For additional details about SAEs, see Table: xx.											

16.2.7.3 Serious Adverse Events

Listing 13: Serious Adverse Events

Adverse Event	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Challenge	Relationship to study procedure	Relationship to Antibiotics	If not related to challenge, antibiotics, or study procedure, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , AE Number:													
Comments:													
Subject ID: , AE Number:													
Comments:													

16.2.8 Individual Laboratory Measurements

Listing 14: Abnormal Laboratory Results

Subject ID	Planned Study Day	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High	If Abnormal, Clinically Significant?

16.2.9.2 Vital Signs

Listing 15: Vital Signs

Subject ID	Study Day	Temperature (°C)	Blood Pressure (mmHg)	Pulse (beats/min)	Weight (kg)	Height (cm)

16.2.9.3 Physical Exam Findings

Listing 16: Physical Exam Findings

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

16.2.9.5 Pregnancy Reports

Listing 17: Pregnancy Test Results

Subject ID	Study Day	Sample Type	Pregnancy Test Result
		Urine/Serum	Positive/Negative

Listing 18: Pregnancy Report

Subject ID	Pregnancy Number	Estimated Study Day of Conception	Pregnancy Confirmation Method	Pregnancy Status	Pregnancy Outcome	Method of Birth	Gestational Age at Delivery	Congenital Anomalies?	Maternal Complications During Pregnancy?	Maternal Complications During Delivery?
			Urine Test/Serum Test/Ultrasound/Other	Ongoing/Outcome Known						