NAVAL MEDICAL RESEARCH COMMAND (NMRC)
DEFENSE INFECTIOUS DISEASES DIRECTORATE (DIDD)
TRANSLATIONAL AND CLINICAL RESEARCH (TraCR) DEPARTMENT

Statistical Analysis Plan
for
PATH Protocol CVIA 088

Study Title:

Controlled Human Infection Model Challenge/Rechallenge: *Shigella flexneri* 2a and *S. sonnei* cross-protective antigens discovery in healthy adults in the United States

Version 1.0
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CVIA 088 Statistical Analysis Plan Revision History

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Protocol Number: CVIA 088 (version 4.2; dated 16 January 2023)
Statistical Analysis Plan (version 1.0)

PATH Statistician

Signed:

DocuSigned by:
Yuxiao Tang
Signer Name: Yuxiao Tang
Signing Reason: I approve this document
Signing Time: 05-Oct-2023 | 07:08 PDT
01E3B2D8EC9547EA8EA3E82F09C8DA89

Yuxiao Tang, PhD
PATH, Center for Vaccine Innovation and Access (CVIA)
2201 Westlake Avenue, Suite 200
Seattle, WA 98121

Principal Biostatistician

Signed:

DocuSigned by:
Chad Porter
Signer Name: Chad Porter
Signing Reason: I approve this document
Signing Time: 05-Oct-2023 | 07:16 PDT
1E303E02D6874702B5263ED08D55F532

Chad Porter, PhD, MPH
TraCR, NMRC
503 Robert Grant Avenue
Silver Spring, MD 20910

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1 Abbreviations and Definitions

AE	Adverse event
AESI	Adverse event of special interest
ALS	Antibody in lymphocyte supernatant
ANOVA	Analysis of variance
AR	Attack rate
ATC	Anatomical Therapeutic Chemical
cfu	Colony-forming units
cGMP	Current Good Manufacturing Practice
CHIM	Controlled human infection model
CI	Confidence interval
CRO	Contract research organization
CSR	Clinical study report
CVIA	Center for Vaccine Innovation and Access
DIDD	Defense Infectious Diseases Directorate
dL	Deciliter
ELISA	Enzyme-linked immunosorbent assay
GMFR	Geometric mean fold-rise
GMT	Geometric mean titer
Hg	Mercury
IBS	Irritable bowel syndrome
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IQR	Interquartile range
LPS	Lipopolysaccharide
MedDRA®	Medical Dictionary for Regulatory Activities®
µg	Microgram
mg	Milligram
mL	Milliliter
NMRC	Naval Medical Research Command
PT	Preferred term
PSRT	Protocol Safety Review Team
PVT	Psychomotor vigilance test
SAE	Serious adverse event
SAP	Statistical analysis plan
SBA	Serum bactericidal antibody
SOC	System organ class
SOP	Standard operating procedure
TD	Travelers' diarrhea
TLFs	Tables, listings, and figures
TraCR	Translational and Clinical Research Department
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

2 Preface

The purpose of this Statistical Analysis Plan (SAP) for the study entitled, "Controlled Human Infection Model Challenge/Rechallenge: *Shigella flexneri* 2a and *S. sonnei* cross-protective antigens discovery in healthy adults in the United States," (PATH protocol CVIA 088; ClinicalTrials.gov Identifier: NCT04992520) is to delineate a robust statistical analysis plan beyond the overview that is included in the study protocol (protocol v4.2; dated 16 January 2023).

This document describes all analyses planned for the study, as well as outlines sample tables, listings, and figures (TLFs) for the final analyses. Additionally, this document contains a review of the study design, general statistical considerations, and comprehensive statistical analysis methods for safety and immunogenicity outcomes. Deviations from this SAP will be described and justified in protocol amendments and/or in the clinical study report (CSR), as appropriate. The reader of this SAP is encouraged to review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

This SAP was completed following guidelines from the following PATH Standard Operating Procedure (SOP) documents:

1. SOP-00045: "Quality Control of Statistical Analysis" (version 1.0; dated 14 May 2021)
2. SOP-00046: "Development of Statistical Analysis Plans" (version 1.0; dated 14 May 2021)

3 Introduction

Shigella is a leading cause of diarrhea-attributed morbidity and mortality globally. *Shigella* accounts for approximately 0.1 to 1.1 million deaths (60% in children under 5 years of age) and 90 to 165 million cases of dysentery annually [1-3]. Among travelers, *Shigella* are a cause of severe travelers' diarrhea (TD) [4]. In adults, shigellosis is linked to several post-infectious sequelae, including irritable bowel syndrome (IBS) and reactive arthritis [5-7]. Additionally, *Shigella* infection is associated with cognitive and physical stunting in children residing in low-income countries, which further highlights the pathogen's associated morbidity.

The *Shigella* controlled human infection model (CHIM) has been used to evaluate the efficacy of investigational *Shigella* vaccines since the studies of Shaughnessy and colleagues in 1946 among prison inmates in Joliet, Illinois [8]. Since then, CHIM trials evaluating *Shigella* vaccine candidates have been conducted at several sites in the United States, mostly with *S. flexneri* 2a (strain 2457T) [7, 9-11] and *S. sonnei* (strain 53G) [9, 10, 12], but also with wild-type and toxin-minus mutants of *S. dysenteriae* type 1 [12-18].

This SAP is for a CHIM study designed to assess the cross-protection and markers of protection after challenge and rechallenge with heterologous serogroups of *Shigella*. In addition to assessing the potential reduction in shigellosis rates following heterologous rechallenge, efforts will be made to identify novel, cross-protective *Shigella* antigens that could enhance vaccine coverage among existing vaccines or serve as stand-alone subunit vaccines.

4 Study Objectives

4.1 Primary Objective

To evaluate the cross-species protection conferred by a rechallenge with a *Shigella* species of a different serotype.

4.2 Secondary Objective

To determine effects of previous challenge when rechallenged with *Shigella* of a different serotype on stool output and clinical symptoms.

4.3 Exploratory Objectives

1. To determine IgG and IgA responses to *Shigella* species-specific lipopolysaccharide (LPS) upon challenge or rechallenge.
2. To utilize novel analyses of immune responses, including antigen arrays, to identify protective immune responses in individuals protected from shigellosis upon challenge or rechallenge.
3. To identify potential protective antigens on the challenge organisms.
4. To confirm that the serum IgG to the O-antigen is a correlate of protection for shigellosis.
5. To assist in the development of international standards against *Shigella* antigens.
6. To measure mucosal and systemic immune responses to experimental infection.
7. To obtain and archive samples for future proteomics, inflammatory marker, microbiome, and/or transcriptomics and systems biology efforts based on the recently published consensus schedule and events table [19].
8. To evaluate the cognitive and sleep impact of acute diarrhea using psychomotor vigilance testing (PVT) and actigraphy.
9. To evaluate serum bactericidal antibody (SBA) titers against *S. flexneri* 2a 2457T and *S. sonnei* 53G (responders defined as ≥4-fold increase in SBA titer at designated time points post-initial challenge and heterologous rechallenge).
10. To evaluate the ability of wearable-collected data to predict clinical and/or microbiological endpoints.

5 Study Endpoints

5.1 Primary Endpoint

The primary endpoint for outcomes following initial challenge and heterologous rechallenge is the onset of shigellosis [20], defined as:

- Severe diarrhea: ≥6 loose (grade 3-5) stools within 24 hours or >800 grams of loose (grade 3-5) stools within any 24-hour window

  OR

- Moderate diarrhea (4 to 5 loose stools within 24 hours or 401-800 grams of loose (grade 3-5) stools within 24 hours) with fever OR with one or more moderate constitutional or enteric symptom OR ≥2 episodes of vomiting within any 24-hour window

  OR

- Dysentery: ≥2 loose stools with gross blood (hemoccult positive) in 24 hours AND fever OR ≥1 moderate constitutional/enteric symptom OR ≥2 episodes of vomiting in 24 hours

Fever: oral temperature ≥38°C confirmed within about 20 minutes

Constitutional/enteric symptoms: nausea, abdominal cramps/pain, myalgia, arthralgia, malaise

5.2 Secondary Endpoints

Secondary endpoints for this study following initial challenge and heterologous rechallenge are:

- Maximum 24-hour stool output
- Percent of participants with severe diarrhea
- Percent of participants with diarrhea of any severity
- Total weight of grade 3-5 stools per participant
- Percent of participants with nausea, vomiting, anorexia, abdominal pain/cramps rated as moderate to severe
- Percent of participants who meet the definition of dysentery
- Mean/median time to onset of diarrhea
- Number of participants with more severe diarrhea (defined as ≥10 loose [grade 3-5] stools within 24 hours or ≥1000 grams of loose [grade 3-5] stools within 24 hours)
- Number of participants with fever
- *Shigella* clinical severity score post-challenge
- Number of colony-forming units (cfu) of the challenge strain per gram of stool

Note: Period of data collection for all secondary endpoints is during the inpatient period.

6 Reactogenicity Events

6.1 Adverse Events (AEs)

Information pertaining to AEs is detailed in Section XIII, part 5 of the study protocol.

6.2 Suspected Adverse Reaction

Information pertaining to suspected adverse reactions is detailed in Section XIII, part 5 of the study protocol.

6.3 Solicited and Anticipated AEs

Information pertaining to solicited and anticipated AEs is detailed in Section XIII, part 5 of the study protocol.

6.4 AEs of Special Interest (AESI)

Information pertaining to AESIs is detailed in Section XIII, part 5 of the study protocol.

6.5 Serious Adverse Events (SAEs)

Information pertaining to SAEs is detailed in Section XIII, part 5 of the study protocol.

6.6 AE Relationship to the Investigational Product

Information pertaining to AE relationships to the investigational product is detailed in Section XIII, part 6 of the study protocol.

6.7 AE Safety Assessments

Information pertaining to AE safety assessments is detailed in Section XIII, part 9 of the study protocol.

7 Study Methods

7.1 Study Design and Plan

Information pertaining to the study design and plan is detailed in Section VIII, parts 1 and 2 of the study protocol.

7.2 Study Population

7.2.1 Selection of Participants

Information pertaining to the selection of participants is detailed in Section IX, part 1 of the study protocol.

7.2.2 Inclusion and Exclusion Criteria

Information pertaining to the inclusion and exclusion criteria is detailed in Section IX, parts 2 and 3 (respectively) of the study protocol.

7.2.3 Continuing Eligibility Criteria to Proceed to Cohort 1B or 2B

Information pertaining to continuing eligibility criteria to proceed to cohort 1B or 2B is detailed in Section IX, part 4 of the study protocol.

7.3 Challenge Administration

7.3.1 Challenge Strains Administered

Participants will be challenged with approximately $1.5x10^3$ cfu of *S. flexneri* 2a strain 2457T or $1.5x10^3$ cfu of *S. sonnei* strain 53G.

S. flexneri 2a strain 2457T is a well-characterized *Shigella* strain that has had the greatest range of doses tested. This specific strain was isolated from a clinically ill patient in Japan in the early 1950s.

S. sonnei strain 53G has previously been used in low inoculum doses; however, a lyophilized preparation of this strain was recently manufactured to simplify the inoculum preparation process.

Both of these strains were manufactured under current Good Manufacturing Practice (cGMP) conditions at the Walter Reed Army Institute of Research (WRAIR) Pilot BioProduction Facility in Silver Spring, MD.

7.3.2 Method of Selecting Eligible Subjects for Second Challenge

Information pertaining to the selection of eligible subjects for a second challenge is detailed in Section XV, part 2 of the study protocol.

7.3.3 Blinding

As all subjects in each cohort will receive the same challenge strain, blinding will not be employed. However, the adjudication of clinical outcomes will be blinded to both strain and cohort. The study statistician and any other designated staff will have access to the unblinded cohort information and will assign new subject IDs that differs from those assigned at enrollment.

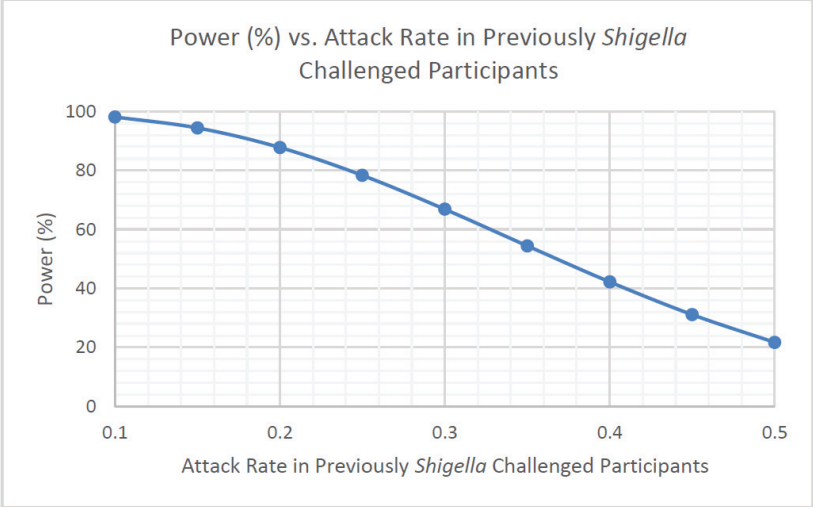
7.4 Immunology Testing

During this study, samples will be collected from all subjects on pre-determined study days to complete the required immunological testing. The following tests will be completed during the study:

1. Serum IgG and IgA responses to *S. flexneri* 2a LPS, *S. flexneri* 2a Invaplex, IpaB, IpaC, and IpaD (2457T strain); *S. sonnei* LPS, *S. sonnei* Invaplex, IpaB, IpaC, and IpaD (53G strain)
2. Antibody in lymphocyte supernatant (ALS) responses to *S. flexneri* 2a LPS, *S. flexneri* 2a Invaplex, IpaB, IpaC, and IpaD (2457T strain); *S. sonnei* LPS, *S. sonnei* Invaplex, IpaB, IpaC, and IpaD (53G strain)
3. Fecal IgA responses to *S. flexneri* 2a LPS, *S. flexneri* 2a Invaplex, IpaB, IpaC, and IpaD (2457T strain); *S. sonnei* LPS, *S. sonnei* Invaplex, IpaB, IpaC, and IpaD (53G strain)
4. Salivary IgA responses to *Shigella* antigens (LPS, IpaB, IpaC, IpaD)

8 Sample Size Considerations

Presuming a shigellosis rate of 70% in naïve participants, a sample size of 16 participants will yield a 95% confidence interval (asymptotic estimates) of 48-92%, while a sample size of 8 participants will yield a 95% confidence interval (asymptotic estimates) of 38-100%. Presuming an ability to pool naïve participants (if the cohorts have a comparable attack rate), a sample size of 19 participants in the previously *S. sonnei* 53G-challenged arm and 16 participants in the *S. flexneri* 2457T-naïve arm provides a >80% power to detect a shigellosis risk difference of 46% presuming a ≥70% attack rate in *Shigella*-naïve participants, while a sample size of 11 participants in the previously *S. flexneri* 2457T-challenged arm and 8 participants in the *S. sonnei* 53G-naïve arm provides a >80% power to detect a shigellosis risk difference of 60% presuming a ≥70% attack rate in *Shigella*-naïve participants (based on a Pearson's chi-squared test for proportional differences and a two-sided *alpha*=0.05). A power curve, corresponding to a sample size of 19 participants in the previously *S. sonnei* 53G-challenged arm and 16 participants in the *S. flexneri* 2457T-naïve arm and an attack rate of 70% in *Shigella*-naïve participants is below:



9 General Study Considerations

9.1 Safety/Full Analysis Population

All subjects who have been screened, consented, and proceeded to receive the challenge strain will serve as the primary analysis population for the safety endpoints. Adverse events will be listed individually and summarized by the Medical Dictionary for Regulatory Activities® (MedDRA®) body system and preferred terms within a body system for each study group. Serious and/or unexpected AEs will also be discussed on a case-by-case basis.

9.2 Per-Protocol Population

The per-protocol population will consist of all subjects in the safety/full analysis population who have no major protocol violations that are determined to potentially interfere with the clinical

assessment. This population will serve as the primary analysis population for the primary and secondary endpoints. Membership in this study population will be determined in a blinded fashion.

9.3 Immunology Population

Analyses will include both qualitative (responder rates) and quantitative results. All challenged subjects with collected post-challenge specimens relevant to each immunologic measure will be included in analyses. This population will serve as the primary analysis population for the immunogenicity endpoints.

9.4 Missing Data

Although data are not anticipated to be missing during the inpatient phase of the study, the potential for subjects to be unable to collect a loose stool during a diarrheal episode could lead to missing data within the stool log and affect the primary endpoint. In this scenario, stools will be designated a weight of 0; however, if the adjudication committee determines that a subject should be characterized as having shigellosis, they would be included in analyses pertaining to that endpoint. Any other missing data due to subject-specific deviations (e.g., failure to return for follow-up or sample collection outside of the timeframe indicated in the protocol) will be documented. These data will be assumed to be missing at random and will be excluded from analyses unless they are identified as an outlier. If a data point is identified as an outlier, sensitivity analyses will be performed to assess the impact of including or excluding the outlier. Significant differences between these sensitivity analyses will be reported.

9.5 Outcome Adjudication

Prior to the closeout of the study, detailed data on stool output and other clinical outcomes will be entered into Advantage eClinical and monitored. To obtain an unbiased determination of the study outcomes, an independent outcome adjudication committee will blindly evaluate challenge outcome data after completion of all inpatient phases of the study. To ensure a blinded review, new subject IDs that differ from those assigned at enrollment will be utilized.

If there are any individuals selected to participate in the challenge phase of the study that do not receive the investigational product, they will be excluded from the information presented. Additional information pertaining to the outcome adjudication committee is detailed in Section XIII, part 11 of the study protocol.

10 Purpose of the Analyses

Analyses will focus on descriptive methods to estimate rates, measures of central tendency (e.g., means, medians, etc.), and data distributions (standard deviations, confidence intervals (CIs), interquartile ranges (IQRs), etc.).

Rates of solicited and unsolicited AEs will be tabulated by level of severity. All rates will be determined with two-sided exact 95% CIs.

During each day of the inpatient period, subjects will be monitored for loose stools (not meeting the diarrhea definition), diarrhea, dysentery, hypovolemia, nausea, vomiting, abdominal cramps/pain, fever, headache, anorexia, arthralgia, bloating, chills, constipation, flatulence, myalgia, lightheadedness, malaise, tenesmus, urgency, abdominal tenderness, abdominal distention, or otherwise abnormal abdominal exam.

Planned statistical evaluations are based on the proportion of subjects meeting prospectively-defined clinical, microbiological, and immunological endpoints. The shigellosis attack rate (AR) will be calculated for all study groups, using the standard definition of: (# with endpoint/# receiving inoculum) x 100%, along with 95% CIs (both asymptotic estimates and exact) for each study group. ARs between *Shigella*-naïve participants and previously challenged participants will be compared using a Pearson's chi-squared or Fisher's exact test, as appropriate. Summary tables will also be created to detail quantitative and temporal features of the illness, such as diarrheal stool frequency and volume, maximum temperature observed, and time to illness and infection. Continuous variables will be analyzed using nonparametric statistics unless assumptions are fulfilled for parametric statistics.

All statistical tests will be interpreted in a two-tailed fashion using an *alpha*=0.05.

10.1 Timing of Analyses

Safety data will be prepared periodically and reviewed by the Protocol Safety Review Team (PSRT) throughout the trial.

After the completion of all inpatient phases of the study for all cohorts, blinded clinical outcome data will be prepared and reviewed by the outcome adjudication committee.

The full set of samples for key immunogenicity variables will be completed at the Day 180 visit.

A final analysis of all data collected will be performed after all data queries have been resolved, membership in the per-protocol population has been determined in a blinded fashion, and the database has been locked.

10.2 Safety Evaluation

10.2.1 Demographics and Other Baseline Characteristics

A summary table of continuous and categorical measures will be presented by study group and overall. A demographics listing will also be prepared, including information on sex, race, ethnicity, and age (in years).

10.2.2 Medical History

Summaries of subjects' pre-existing medical conditions will be prepared; individual subject listings will also be prepared.

10.2.3 Concomitant Medications

Any medications that were taken either prior to or during the study will be coded according to the Anatomical Therapeutic Chemical (ATC) classification system using the World Health Organization (WHO) Drug Dictionary. Summaries as well as individual subject listings will be prepared.

10.2.4 Vital Signs and Physical Evaluations

Systolic and diastolic blood pressure (mmHg), oral temperature (°F), and heart rate (beats/minute) will be obtained multiple times daily throughout the inpatient period and at designated study visits per the study schedule.

A complete physical exam will be conducted during the screening visit and on Day -2 or -1 as part of the screening process. Focused physical exams (symptom focused) will be conducted prior to receipt of any challenge product, daily during the inpatient stay, and as needed during the outpatient visits. A table summarizing the occurrence of abnormal physical exam findings will be presented by body system and study group.

10.2.5 Safety Analyses

Table listings for AEs outlined in Section 6 of this SAP will be created to show the AE(s) a subject experiences, the onset date, the end date, the severity, the relationship to the challenge strain and/or antibiotic administration, and the outcome of the listed AE.

Additionally, all safety data will be listed individually and summarized by body system and preferred term within a body system for each study group. Serious and/or unexpected AEs will also be described on a case-by-case basis. For the tabulation of AEs by body system, a subject will be counted only once in a given body system. For example, a subject reporting nausea and diarrhea will be reported as one subject, but the symptoms will be listed as two separate AEs within the class. Therefore, the total number of AEs reported within a body system may exceed the number of subjects within the body system reporting AEs.

The proportion of all subjects with each AE will be summarized with a point estimate for percent and exact 95% CIs. Summary tables describing the number and percentage of subjects who experience each AE will be created. In addition, tables will be prepared to list each AE, the number of subjects experiencing an event at least once, and the proportion of subjects with an AE(s). AEs will be divided into defined severity grades (mild, moderate, severe, or potentially life threatening). The tables will also differentiate the relationship of AEs to the investigational product.

10.3 Immunogenicity Analyses

Immunogenicity analyses will include both qualitative (responder rates) and quantitative (using $\log_{10}$-transformed values) outcomes.

Graphical displays of immune responses will include the following:

1. Scatter plots of peak fold-rise in antibody titer by study group for each antigen (serology and fecal IgA)
2. Salivary IgA responses
3. Response kinetics (group geometric mean titer [GMT] at each study time point to assess multiple dose effect)

Descriptive statistics (including mean and standard deviation of $\log_{10}$ titers, GMT and 95% CIs, median, and IQR) will be tabulated by cohort, challenge status (initial challenge and secondary challenge), and time point. Geometric mean fold-rises (GMFRs) from baseline will also be calculated and summarized.

Between-group comparisons will be examined with nonparametric tests (Kruskal-Wallis test for continuous data and Fisher's exact test for categorical data), unless assumptions are fulfilled for ANOVA or Pearson's chi-squared test. Nonparametric paired t-tests (Wilcoxon paired signed-rank test) will be used to compare individual post-challenge to baseline responses within each study group, unless assumptions are fulfilled for paired t-tests. Comparisons of ALS responses post-challenge will be performed using the Kruskal-Wallis test. All statistical tests will be interpreted in a two-tailed fashion using *alpha*=0.05.

Immunologic Responder Definitions

Serology: An immunologic responder is defined as any subject who demonstrates a ≥4-fold rise in reciprocal serum enzyme-linked immunosorbent assay (ELISA) antibody titers from baseline. A 4-fold rise is calculated by dividing the post-challenge reciprocal endpoint titer by the baseline reciprocal endpoint titer. All statistical analyses will be performed on $\log_{10}$-transformed titer values. Titers will be displayed graphically as $\log_{10}$ reciprocal endpoint titers or geometric mean titers.

Antibody in Lymphocyte Supernatant (ALS): An immunologic responder is any subject who demonstrates a ≥4-fold rise in reciprocal titers from baseline. A 4-fold rise is calculated by dividing the post-challenge reciprocal endpoint titer by the baseline reciprocal endpoint titer. Once a subject is defined as an 'immunologic responder', that person is permanently categorized as a 'RESPONDER'. All statistical analyses will be performed on $\log_{10}$-transformed titer values. Titers will be displayed graphically as $\log_{10}$ reciprocal endpoint titers or geometric mean titers.

Fecal IgA: Total IgA content in the fecal extract samples will be determined by a modified ELISA method using commercial purified total IgA standard. Specimens with an IgA concentration <10 µg/mL will be excluded from all assessments of responder rates. Specific antibody levels in the fecal extracts will be determined using similar ELISA methods to those described above. Fecal antibodies will be reported as adjusted endpoint titers and calculated by dividing the endpoint titer by the IgA concentration of the sample. A subject with a ≥4-fold increase in the specific IgA per total IgA content between pre- and any post-challenge specimens is considered an immunologic responder. All statistical analyses will be performed on $\log_{10}$-transformed titer values.

Salivary IgA: Total IgA content in the salivary extract samples will be determined by a modified ELISA method using commercial purified total IgA standard. Specimens with an IgA concentration <10 µg/mL will be excluded from all assessments of responder rates. Specific antibody levels in the salivary extracts will be determined using similar ELISA methods to those described above. Salivary antibodies will be reported as adjusted endpoint titers. A subject with a ≥4-fold increase in the specific IgA per total IgA content between pre- and any post-challenge specimens is considered an immunologic responder. All statistical analyses will be performed on $\log_{10}$-transformed titer values.

In addition to the analyses detailed above, several post hoc analyses will be performed in an effort to further characterize the safety and immunogenicity of the study products. Estimated parameters not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant digits.

11 General Statistical Considerations

All analyses will be grouped by cohort (1A, 1B, 2A, 2B). Generally, all data will be listed by cohort and subject. All summary tables will be structured with a column for each cohort and include an annotation for the total population size relevant to the table.

12 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as '<0.001'. Means, standard deviations, and any other statistics other than quantiles will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places.

13 Technical Details

Statistical analyses will be performed using SAS v9.4 or newer for Windows (The SAS Institute, Cary, NC) and RStudio 2022.02.0 + 443 "Prairie Trillium" Release for Windows.

14 Summary of Changes to Planned Analyses Outlined in Protocol

The analysis population definitions were modified from those originally outlined in the study protocol to better align with the planned study analyses.

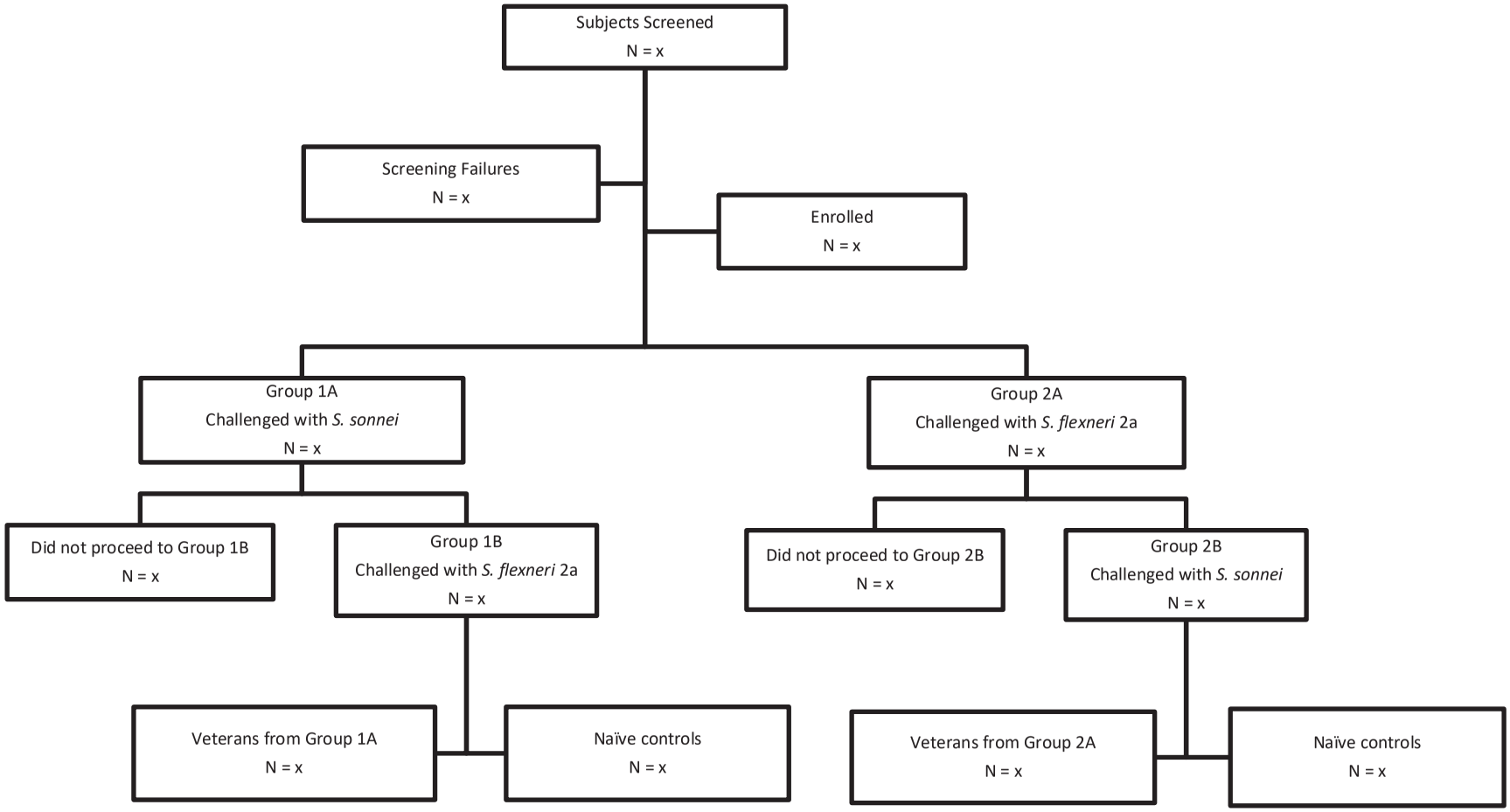
15 Appendices

15.1 Sample Data Tables and Figures for Final Clinical Study Report

Sample data tables and figures to be included in the final clinical study report are included below to guide the analysis and data presentation. Final tables and figures may be modified to optimize data presentation.

Figures

Figure 1: Disposition of Subjects



Listings

Listing 1: Demographics - Safety Population

Subject ID	Sex	Race	Ethnicity	Age (years)

Listing 2: Pre-Existing Medical Conditions - Safety Population

Subject ID	Study Group	Medical History Term	Start Date	End Date

Listing 3: Solicited Adverse Events - Safety Population

Subject ID	Study Group	AE Description	MedDRA® SOC	MedDRA® Preferred Term	Start Date	End Date	Severity	Relationship to Challenge	Relationship to Antibiotics	Outcome

AE: adverse event; MedDRA®: Medical Dictionary for Regulatory Activities; SOC: system organ class

Tables with similar format to Listing 3:

Listing 4: Unsolicited Adverse Events - Safety Population

Listing 5: Serious Adverse Events - Safety Population

Listing 6: Vital Signs by Subject - Safety Population

Subject ID	Study Group	Study Day	Date	Time	Temperature (°F)	Pulse (bpm)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)

BP: blood pressure

Listing 7: Listing of Hematology Laboratory Values by Subject - Safety Population

Subject ID	Study Group	Study Day	Date	Leukocytes (cells/mm^3)	Neutrophils (cells/mm^3)	Lymphocytes (cells/mm^3)	Hemoglobin (g/dL)	Platelets (cells/mm^3)	Eosinophils (cells/mm^3)

Listing 8: Listing of Chemistry Laboratory Values by Subject - Safety Population

Subject ID	Study Group	Study Day	Date	AST (u/L)	ALT (u/L)	Creatinine (mg/dL)	Sodium (mEq/L)	Potassium (mEq/L)	BUN (mg/dL)	Glucose (mg/dL)

Listing 9: Listing of Concomitant Medications by Subject - Safety Population

Subject ID	Study Group	Medication	Dose	Unit	Frequency	Route	Date Started	Date Stopped	Indication

Listing 10: Listing of Subject-Specific Protocol Deviations - Safety Population

Subject ID	Study Group	Date	Protocol Deviation	Reason for Deviation	Resulted in AE	Deviation Category	Deviation Resolution

AE: adverse event

Listing 11: Listing of Non-Subject-Specific Protocol Deviations - Safety Population

Date	Protocol Deviation	Reason for Deviation	Resulted in AE	Deviation Category	Deviation Resolution

AE: adverse event

Listing 12: Subjects Withdrawn or Lost to Follow-Up - Safety Population

Subject ID	Date of Last Visit	Reason for Withdrawal/Loss to Follow-Up

Listing 13: Stool Log Listing - Safety Population

Subject ID	Study Group	Study Day	Collection Date	Collection Time	Grade	Weight (g)	Gross Blood Present	Culture Result

Listing 14: Challenge Administration - Safety Population

Subject ID	Study Group	Challenge Strain	Dose Date	Dose Prep Time	Confirmed Dose (cfu)	Time Buffer Administered	Time Challenge Administered

Data Tables

Table 1: Demographics and Baseline Characteristics by Treatment Group - All Enrolled Subjects

	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	All Subjects (N=X)
Sex [n (%)]							
Male							
Female							
Ethnicity [n (%)]							
Not Hispanic or Latino							
Hispanic or Latino							
Not Reported							
Unknown							
Race [n (%)]							
American Indian or Alaska Native							
Asian							
Native Hawaiian or Other Pacific Islander							
Black or African American							
White							
Multi-Racial							
Unknown							
Age (years)							
Mean (SD)							
Median							
Min/Max							

SD: standard deviation

Table 2: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[1]

[1] More than one criterion may be marked per subject.

Table 3: Concomitant Medications by WHO Drug Classification - Safety Population [n (%)]

Anatomical Therapeutic Chemical	Medication Name	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	All Subjects (N=X)
[ATC 1]	[Medication 1]							
	[Medication 2]							
	[Medication 3]							
[ATC 2]	[Medication 1]							
	[Medication 2]							
	[Medication 3]							

Table 4: Pre-Existing Medical Conditions by Treatment Group - Safety Population [n (%)]

Medical Condition	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	All Subjects (N=X)

Table 5: Adverse Events by MedDRA® System Organ Class (SOC), Preferred Term (PT), and Treatment Group Coded as 'Related' to Challenge - Safety Population [n (%)]

System Organ Class	Preferred Term	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	All Subjects (N=X)	P-Value*
[SOC 1]	[PT 1]								
	[PT 2]								
	[PT 3]								
[SOC 2]	[PT 1]								
	[PT 2]								
	[PT 3]								

*Between-group comparisons completed using Chi-squared analyses.

Table with similar format to Table 5:

Table 6: Adverse Events by MedDRA® System Organ Class (SOC), Preferred Term (PT), and Treatment Group Coded as 'Unrelated' to Challenge - Safety Population [n (%)]

Table 7: Severity of Solicited and Anticipated Adverse Events (Group 1A) - Per-Protocol Population [n (%)]

	Group 1A (N=X)					
	None	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Abdominal Cramps/Pain						
Anorexia						
Arthralgia						
Bloating						
Chills						
Constipation						
Flatulence						
Myalgia						
Headache						
Lightheadedness						
Malaise						
Nausea						
Tenesmus						
Urgency						
Diarrhea						
Dysentery						
Hypovolemia						
Fever						
Vomiting						

Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: potentially life-threatening

Table with similar format to Table 7:

Table 8: Severity of Solicited and Anticipated Adverse Events (Group 2A) - Per-Protocol Population [n (%)]

Table 9: Severity of Solicited and Anticipated Adverse Events (Group 1B) - Per-Protocol Population [n (%)]

	Group 1B, Naïve (N=X)						Group 1B, Veteran (N=X)					
	None	Grade 1	Grade 2	Grade 3	Grade 4	Total	None	Grade 1	Grade 2	Grade 3	Grade 4	Total
Abdominal Cramps/Pain												
Anorexia												
Arthralgia												
Bloating												
Chills												
Constipation												
Flatulence												
Myalgia												
Headache												
Lightheadedness												
Malaise												
Nausea												
Tenesmus												
Urgency												
Diarrhea												
Dysentery												
Hypovolemia												
Fever												
Vomiting												

Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: potentially life-threatening

Table with similar format to Table 9:

Table 10: Severity of Solicited and Anticipated Adverse Events (Group 2B) - Per-Protocol Population [n (%)]

Table 11: Rates of Shigellosis (95% CI) and Constitutional/Enteric Symptoms Following *Shigella* Challenge - Per-Protocol Population

	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	All Subjects (N=X)
Shigellosis							
Any Diarrhea							
Mild Diarrhea							
Moderate Diarrhea							
Severe Diarrhea							
More Severe Diarrhea							
Dysentery							
Fever (any severity)							
Moderate/Severe Abdominal Pain/Cramps							
Moderate/Severe Nausea							
Moderate/Severe Vomiting							
Moderate/Severe Anorexia							
Moderate/Severe Myalgia							
Moderate/Severe Arthralgia							
Moderate/Severe Malaise							

Table 12: Summary of Quantitative and Temporal Features of Illness - Per-Protocol Population

	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	All Subjects (N=X)
Maximum number of loose stools in 24h	Mean							
	Median							
	SD							
	Range							
Maximum volume of loose stools in 24h (g)	Mean							
	Median							
	SD							
	Range							
Total number of loose stools	Mean							
	Median							
	SD							
	Range							
Total volume of loose stools (g)	Mean							
	Median							
	SD							
	Range							
Maximum temperature (°F)	Mean							
	Median							
	SD							
	Range							
Time to diarrhea onset	Mean							
	Median							
	SD							
	Range							
Time to first *Shigella*-positive stool	Mean							
	Median							
	SD							

	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	All Subjects (N=X)
	Range							
Shigella clinical severity score	Mean							
	Median							
	SD							
	Range							

SD: standard deviation

15.2 Sample Data Tables and Figures for Exploratory Analyses

Sample data tables and figures for exploratory analyses are included below to guide the analysis and data presentation. Final tables and figures may be modified to optimize data presentation.

Listings

Listing 15: Listing of Serologic IgG Responses to *S. flexneri* 2a Invaplex by Subject - Immunology Population

Subject ID	Study Group	Baseline	Day 8	Day 15	Day 29	Day 57	Day 90	Day 180

Tables with similar format to Listing 15:

Listing 16: Listing of Serologic IgA Responses to *S. flexneri* 2a Invaplex by Subject - Immunology Population

Listing 17: Listing of Serologic IgG Responses to *S. flexneri* 2a LPS by Subject - Immunology Population

Listing 18: Listing of Serologic IgA Responses to *S. flexneri* 2a LPS by Subject - Immunology Population

Listing 19: Listing of Serologic IgG Responses to *S. flexneri* 2a IpaB by Subject - Immunology Population

Listing 20: Listing of Serologic IgA Responses to *S. flexneri* 2a IpaB by Subject - Immunology Population

Listing 21: Listing of Serologic IgG Responses to *S. flexneri* 2a IpaC by Subject - Immunology Population

Listing 22: Listing of Serologic IgA Responses to *S. flexneri* 2a IpaC by Subject - Immunology Population

Listing 23: Listing of Serologic IgG Responses to *S. flexneri* 2a IpaD by Subject - Immunology Population

Listing 24: Listing of Serologic IgA Responses to *S. flexneri* 2a IpaD by Subject - Immunology Population

Listing 25: Listing of Serologic IgG Responses to *S. sonnei* Invaplex by Subject - Immunology Population

Listing 26: Listing of Serologic IgA Responses to *S. sonnei* Invaplex by Subject - Immunology Population

Listing 27: Listing of Serologic IgG Responses to *S. sonnei* LPS by Subject - Immunology Population

Listing 28: Listing of Serologic IgA Responses to *S. sonnei* LPS by Subject - Immunology Population

Listing 29: Listing of Serologic IgG Responses to *S. sonnei* IpaB by Subject - Immunology Population

Listing 35: Listing of Antibody in Lymphocyte Supernatant (ALS) IgG Responses to *S. flexneri* 2a Invaplex by Subject - Immunology Population

Subject ID	Study Group	Baseline	Day 4	Day 6	Day 8

Tables with similar format to Listing 35:

Listing 36: Listing of ALS IgA Responses to *S. flexneri* 2a Invaplex by Subject - Immunology Population

Listing 37: Listing of ALS IgG Responses to *S. flexneri* 2a LPS by Subject - Immunology Population

Listing 38: Listing of ALS IgA Responses to *S. flexneri* 2a LPS by Subject - Immunology Population

Listing 39: Listing of ALS IgG Responses to *S. flexneri* 2a IpaB by Subject - Immunology Population

Listing 40: Listing of ALS IgA Responses to *S. flexneri* 2a IpaB by Subject - Immunology Population

Listing 41: Listing of ALS IgG Responses to *S. flexneri* 2a IpaC by Subject - Immunology Population

Listing 42: Listing of ALS IgA Responses to *S. flexneri* 2a IpaC by Subject - Immunology Population

Listing 43: Listing of ALS IgG Responses to *S. flexneri* 2a IpaD by Subject - Immunology Population

Listing 44: Listing of ALS IgA Responses to *S. flexneri* 2a IpaD by Subject - Immunology Population

Listing 45: Listing of ALS IgG Responses to *S. sonnei* Invaplex by Subject - Immunology Population

Listing 46: Listing of ALS IgA Responses to *S. sonnei* Invaplex by Subject - Immunology Population

Listing 47: Listing of ALS IgG Responses to *S. sonnei* LPS by Subject - Immunology Population

Listing 48: Listing of ALS IgA Responses to *S. sonnei* LPS by Subject - Immunology Population

Listing 49: Listing of ALS IgG Responses to *S. sonnei* IpaB by Subject - Immunology Population

Listing 50: Listing of ALS IgA Responses to *S. sonnei* IpaB by Subject - Immunology Population

Listing 55: Listing of Fecal IgA Responses to *S. flexneri* 2a Invaplex by Subject - Immunology Population

Subject ID	Study Group	Baseline	Day 4	Day 8	Day 15	Day 29

Tables with similar format to Listing 55:

Listing 56: Listing of Fecal IgA Responses to *S. flexneri* 2a LPS by Subject - Immunology Population

Listing 57: Listing of Fecal IgA Responses to *S. flexneri* 2a IpaB by Subject - Immunology Population

Listing 58: Listing of Fecal IgA Responses to *S. flexneri* 2a IpaC by Subject - Immunology Population

Listing 59: Listing of Fecal IgA Responses to *S. flexneri* 2a IpaD by Subject - Immunology Population

Listing 60: Listing of Fecal IgA Responses to *S. sonnei* Invaplex by Subject - Immunology Population

Listing 61: Listing of Fecal IgA Responses to *S. sonnei* LPS by Subject - Immunology Population

Listing 62: Listing of Fecal IgA Responses to *S. sonnei* IpaB by Subject - Immunology Population

Listing 63: Listing of Fecal IgA Responses to *S. sonnei* IpaC by Subject - Immunology Population

Listing 64: Listing of Fecal IgA Responses to *S. sonnei* IpaD by Subject - Immunology Population

Listing 65: Salivary IgA Responses to *S. flexneri* 2a Invaplex, Listing of Values by Subject - Immunology Population

Subject ID	Study Group	Baseline	Day 2	Day 4	Day 6	Day 8	Day 15	Day 29	Day 57

Tables with similar format to - **Immunology Population**

Listing 65:

Listing 66: Listing of Salivary IgA Responses to *S. flexneri* 2a LPS by Subject - Immunology Population

Listing 67: Listing of Salivary IgA Responses to *S. flexneri* 2a IpaB by Subject - Immunology Population

Listing 68: Listing of Salivary IgA Responses to *S. flexneri* 2a IpaC by Subject - Immunology Population

Listing 69: Listing of Salivary IgA Responses to *S. flexneri* 2a IpaD by Subject - Immunology Population

Listing 70: Listing of Salivary IgA Responses to *S. sonnei* Invaplex by Subject - Immunology Population

Listing 71: Listing of Salivary IgA Responses to *S. sonnei* LPS by Subject - Immunology Population

Listing 72: Listing of Salivary IgA Responses to *S. sonnei* IpaB by Subject - Immunology Population

Listing 73: Listing of Salivary IgA Responses to *S. sonnei* IpaC by Subject - Immunology Population

Listing 74: Listing of Salivary IgA Responses to *S. sonnei* IpaD by Subject - Immunology Population

Data Tables

Table 13: Number of Immunology Samples Collected and Analyzed (Group 1A)[1] - Immunology Population

Assay	Baseline[2]	Day 2	Day 4	Day 6	Day 8	Day 15	Day 29	Day 57	Day 90	Day 180
Serology										
S. flexneri 2a Invaplex IgA										
S. flexneri 2a Invaplex IgG										
S. flexneri 2a LPS IgA										
S. flexneri 2a LPS IgG										
S. flexneri 2a IpaB IgA										
S. flexneri 2a IpaB IgG										
S. flexneri 2a IpaC IgA										
S. flexneri 2a IpaC IgG										
S. flexneri 2a IpaD IgA										
S. flexneri 2a IpaD IgG										
S. sonnei Invaplex IgA										
S. sonnei Invaplex IgG										
S. sonnei LPS IgA										
S. sonnei LPS IgG										
S. sonnei IpaB IgA										
S. sonnei IpaB IgG										
S. sonnei IpaC IgG										
S. sonnei IpaC IgA										
S. sonnei IpaD IgA										
S. sonnei IpaD IgG										
ALS										
S. flexneri 2a Invaplex IgA										
S. flexneri 2a Invaplex IgG										
S. flexneri 2a LPS IgA										
S. flexneri 2a LPS IgG										
S. flexneri 2a IpaB IgA										

Assay	Baseline[2]	Day 2	Day 4	Day 6	Day 8	Day 15	Day 29	Day 57	Day 90	Day 180
S. flexneri 2a IpaB IgG										
S. flexneri 2a IpaC IgA										
S. flexneri 2a IpaC IgG										
S. flexneri 2a IpaD IgA										
S. flexneri 2a IpaD IgG										
S. sonnei Invaplex IgA										
S. sonnei Invaplex IgG										
S. sonnei LPS IgA										
S. sonnei LPS IgG										
S. sonnei IpaB IgA										
S. sonnei IpaB IgG										
S. sonnei IpaC IgG										
S. sonnei IpaC IgA										
S. sonnei IpaD IgA										
S. sonnei IpaD IgG										
Fecal										
S. flexneri 2a Invaplex IgA										
S. flexneri 2a LPS IgA										
S. flexneri 2a IpaB IgA										
S. flexneri 2a IpaC IgA										
S. flexneri 2a IpaD IgA										
S. sonnei Invaplex IgA										
S. sonnei LPS IgA										
S. sonnei IpaB IgA										
S. sonnei IpaC IgA										
S. sonnei IpaD IgA										
Salivary										
S. flexneri 2a Invaplex IgA										
S. flexneri 2a LPS IgA										
S. flexneri 2a IpaB IgA										

Assay	Baseline[2]	Day 2	Day 4	Day 6	Day 8	Day 15	Day 29	Day 57	Day 90	Day 180
S. flexneri 2a IpaC IgA										
S. flexneri 2a IpaD IgA										
S. sonnei Invaplex IgA										
S. sonnei LPS IgA										
S. sonnei IpaB IgA										
S. sonnei IpaC IgA										
S. sonnei IpaD IgA										

[1] Analyzed by the lab and data available.

[2] Most recent observation prior to challenge.

IgA: immunoglobulin A; IgG: immunoglobulin G; LPS: lipopolysaccharide; IpaB: invasin plasmid antigen B; IpaC: invasin plasmid antigen C; IpaD: invasin plasmid antigen D; ALS: antibody in lymphocyte supernatant

Tables with similar format to Table 13:

Table 14: Number of Immunology Samples Collected and Analyzed (Group 1B) - Immunology Population

Table 15: Number of Immunology Samples Collected and Analyzed (Group 2A) - Immunology Population

Table 16: Number of Immunology Samples Collected and Analyzed (Group 2B) - Immunology Population

Table 17: Serologic IgG Responses to *S. flexneri* 2a Invaplex, Descriptive Statistics by Study Day and Study Group - Immunology Population*

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)
Baseline	n	xx					
	Mean	xxx.x					
	Median	xxxx					
	SD	xxx.x					
	Range	xxxx, xxxx					
Day 8	n						
	Mean						
	Median						
	SD						
	Range						
Day 15	n						
	Mean						
	Median						
	SD						
	Range						
Day 29	n						
	Mean						
	Median						
	SD						
	Range						
Day 57	n						
	Mean						
	Median						
	SD						
	Range						

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)
Day 90	n						
	Mean						
	Median						
	SD						
	Range						
Day 180	n						
	Mean						
	Median						
	SD						
	Range						

IgG: immunoglobulin G; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; SD: standard deviation

*Log_{10} titers used to summarize these data.

Tables with similar format to Table 17:

Table 18: Serologic IgA Responses to *S. flexneri* 2a Invaplex, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 19: Serologic IgG Responses to *S. flexneri* 2a LPS, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 20: Serologic IgA Responses to *S. flexneri* 2a LPS, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 21: Serologic IgG Responses to *S. flexneri* 2a IpaB, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 22: Serologic IgA Responses to *S. flexneri* 2a IpaB, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 23: Serologic IgG Responses to *S. flexneri* 2a IpaC, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 37: Antibody in Lymphocyte Supernatant (ALS) IgG Responses to *S. flexneri* 2a Invaplex, Descriptive Statistics by Study Day and Study Group - Immunology Population*

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)
Baseline	n	xx					
	Mean	xxx.x					
	Median	xxxx					
	SD	xxx.x					
	Range	xxxx, xxxx					
Day 4	n						
	Mean						
	Median						
	SD						
	Range						
Day 6	n						
	Mean						
	Median						
	SD						
	Range						
Day 8	n						
	Mean						
	Median						
	SD						
	Range						

IgG: immunoglobulin G; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; SD: standard deviation

*Log_{10} titers used to summarize these data.

Tables with similar format to Table 37:

Table 38: ALS IgA Responses to *S. flexneri* 2a Invaplex, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 39: ALS IgG Responses to *S. flexneri* 2a LPS, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 40: ALS IgA Responses to *S. flexneri* 2a LPS, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 41: ALS IgG Responses to *S. flexneri* 2a IpaB, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 42: ALS IgA Responses to *S. flexneri* 2a IpaB, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 43: ALS IgG Responses to *S. flexneri* 2a IpaC, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 44: ALS IgA Responses to *S. flexneri* 2a IpaC, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 45: ALS IgG Responses to *S. flexneri* 2a IpaD, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 46: ALS IgA Responses to *S. flexneri* 2a IpaD, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 47: ALS IgG Responses to *S. sonnei* Invaplex, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 48: ALS IgA Responses to *S. sonnei* Invaplex, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 49: ALS IgG Responses to *S. sonnei* LPS, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 50: ALS IgA Responses to *S. sonnei* LPS, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 51: ALS IgG Responses to *S. sonnei* IpaB, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 57: Fecal IgA Responses to *S. flexneri* 2a Invaplex, Descriptive Statistics by Study Day and Study Group - Immunology Population*

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)
Baseline	n	xx					
	Mean	xxx.x					
	Median	xxxx					
	SD	xxx.x					
	Range	xxxx, xxxx					
Day 4	n						
	Mean						
	Median						
	SD						
	Range						
Day 8	n						
	Mean						
	Median						
	SD						
	Range						
Day 15	n						
	Mean						
	Median						
	SD						
	Range						
Day 29	n						
	Mean						
	Median						
	SD						
	Range						

IgA: immunoglobulin A; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; SD: standard deviation

*Log_{10} titers used to summarize these data.

Tables with similar format to Table 57:

Table 58: Fecal IgA Responses to *S. flexneri* 2a LPS, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 59: Fecal IgA Responses to *S. flexneri* 2a IpaB, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 60: Fecal IgA Responses to *S. flexneri* 2a IpaC, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 61: Fecal IgA Responses to *S. flexneri* 2a IpaD, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 62: Fecal IgA Responses to *S. sonnei* Invaplex, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 63: Fecal IgA Responses to *S. sonnei* LPS, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 64: Fecal IgA Responses to *S. sonnei* IpaB, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 65: Fecal IgA Responses to *S. sonnei* IpaC, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 66: Fecal IgA Responses to *S. sonnei* IpaD, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 67: Salivary IgA Responses to *S. flexneri* 2a Invaplex, Descriptive Statistics by Study Day and Study Group - Immunology Population*

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)
Baseline	n	xx					
	Mean	xxx.x					
	Median	xxxx					
	SD	xxx.x					
	Range	xxxx, xxxx					
Day 2	n						
	Mean						
	Median						
	SD						
	Range						
Day 4	n						
	Mean						
	Median						
	SD						
	Range						
Day 6	n						
	Mean						
	Median						
	SD						
	Range						
Day 8	n						
	Mean						
	Median						
	SD						
	Range						
Day 15	n						

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)
	Mean						
	Median						
	SD						
	Range						
Day 29	n						
	Mean						
	Median						
	SD						
	Range						
Day 57	n						
	Mean						
	Median						
	SD						
	Range						

IgA: immunoglobulin A; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; SD: standard deviation

*Log_{10} titers used to summarize these data.

Tables with similar format to Table 67:

Table 68: Salivary IgA Responses to *S. flexneri* 2a LPS, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 69: Salivary IgA Responses to *S. flexneri* 2a IpaB, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 70: Salivary IgA Responses to *S. flexneri* 2a IpaC, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 71: Salivary IgA Responses to *S. flexneri* 2a IpaD, Descriptive Statistics by Study Day and Study Group - Immunology Population

Table 77: Serologic Responses to *S. flexneri* 2a Invaplex, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
Serum IgA								
Baseline	n	xx						x.xxxx
	GMT	xxxx						
	95% CI	xxxx, xxxx						
Day 8	n	xx						
	GMT	xxxx						
	95% CI	xxxx, xxxx						
	GMFR	xxxx						
	GMFR 95% CI	xxxx, xxxx						
Day 15	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 29	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 57	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 90	n							

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 180	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Serum IgG								
Baseline	n							
	GMT							
	95% CI							
Day 8	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 15	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 29	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
Day 57	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 90	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 180	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							

IgA: immunoglobulin A; IgG: immunoglobulin G; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; GMT: geometric mean titer; CI: confidence interval; GMFR: geometric mean fold-rise from baseline

[1]P-values are from ANOVA tests of differences between groups in mean log titers.

Tables with similar format to Table 77:

Table 78: Serologic Responses to *S. flexneri* 2a LPS, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 79: Serologic Responses to *S. flexneri* 2a IpaB, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 80: Serologic Responses to *S. flexneri* 2a IpaC, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 81: Serologic Responses to *S. flexneri* 2a IpaD, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 87: ALS Responses to *S. flexneri* 2a Invaplex, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
ALS IgA								
Baseline	n	xx						x.xxxx
	GMT	xxxx						
	95% CI	xxxx, xxxx						
Day 4	n	xx						
	GMT	xxxx						
	95% CI	xxxx, xxxx						
	GMFR	xxxx						
	GMFR 95% CI	xxxx, xxxx						
Day 6	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 8	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
ALS IgG								
Baseline	n							
	GMT							
	95% CI							
Day 4	n							
	GMT							

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 6	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 8	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							

ALS: antibody in lymphocyte supernatant; IgA: immunoglobulin A; IgG: immunoglobulin G; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; GMT: geometric mean titer; CI: confidence interval; GMFR: geometric mean fold-rise from baseline
[1]P-values are from ANOVA tests of differences between groups in mean log titers.

Tables with similar format to Table 87:

Table 88: ALS Responses to *S. flexneri* 2a LPS, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 89: ALS Responses to *S. flexneri* 2a IpaB, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 90: ALS Responses to *S. flexneri* 2a IpaC, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 91: ALS Responses to *S. flexneri* 2a IpaD, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 92: ALS Responses to *S. sonnei* Invaplex, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 97: Fecal IgA Responses to *S. flexneri* 2a Invaplex, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
Baseline	n	xx						x.xxxx
	GMT	xxxx						
	95% CI	xxxx, xxxx						
Day 4	n	xx						
	GMT	xxxx						
	95% CI	xxxx, xxxx						
	GMFR	xxxx						
	GMFR 95% CI	xxxx, xxxx						
Day 8	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 15	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 29	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							

IgA: immunoglobulin A; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; GMT: geometric mean titer; CI: confidence interval; GMFR: geometric mean fold-rise from baseline

[1]P-values are from ANOVA tests of differences between groups in mean log titers.

Tables with similar format to Table 97:

Table 98: Fecal IgA Responses to *S. flexneri* 2a LPS, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 99: Fecal IgA Responses to *S. flexneri* 2a IpaB, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 100: Fecal IgA Responses to *S. flexneri* 2a IpaC, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 101: Fecal IgA Responses to *S. flexneri* 2a IpaD, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 102: Fecal IgA Responses to *S. sonnei* Invaplex, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 103: Fecal IgA Responses to *S. sonnei* LPS, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 104: Fecal IgA Responses to *S. sonnei* IpaB, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 105: Fecal IgA Responses to *S. sonnei* IpaC, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 106: Fecal IgA Responses to *S. sonnei* IpaD, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 107: Salivary IgA Responses to *S. flexneri* 2a Invaplex, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
Baseline	n	xx						x.xxxx
	GMT	xxxx						
	95% CI	xxxx, xxxx						
Day 2	n	xx						
	GMT	xxxx						
	95% CI	xxxx, xxxx						
	GMFR	xxxx						
	GMFR 95% CI	xxxx, xxxx						
Day 4	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 6	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 8	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 15	n							
	GMT							

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 29	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							
Day 57	n							
	GMT							
	95% CI							
	GMFR							
	GMFR 95% CI							

IgA: immunoglobulin A; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; GMT: geometric mean titer; CI: confidence interval; GMFR: geometric mean fold-rise from baseline

[1]P-values are from ANOVA tests of differences between groups in mean log titers.

Tables with similar format to Table 107:

Table 108: Salivary IgA Responses to *S. flexneri* 2a LPS, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 109: Salivary IgA Responses to *S. flexneri* 2a IpaB, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 110: Salivary IgA Responses to *S. flexneri* 2a IpaC, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 111: Salivary IgA Responses to *S. flexneri* 2a IpaD, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 112: Salivary IgA Responses to *S. sonnei* Invaplex, Geometric Mean Titer by Study Day and Study Group - Immunology Population

Table 117: Serologic Responses to *S. flexneri* 2a Invaplex, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
Serum IgA								
Day 8	n	xx						x.xxxx
	Responder %	xx.x						
	95% CI	xx.x, xx.x						
Day 15	n							
	Responder %							
	95% CI							
Day 29	n							
	Responder %							
	95% CI							
Day 57	n							
	Responder %							
	95% CI							
Day 90	n							
	Responder %							
	95% CI							
Day 180	n							
	Responder %							
	95% CI							
Serum IgG								
Day 8	n							
	Responder %							
	95% CI							
Day 15	n							
	Responder %							

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
	95% CI							
Day 29	n							
	Responder %							
	95% CI							
Day 57	n							
	Responder %							
	95% CI							
Day 90	n							
	Responder %							
	95% CI							
Day 180	n							
	Responder %							
	95% CI							

IgA: immunoglobulin A; IgG: immunoglobulin G; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; Responder defined as ≥4-fold increase in titer from baseline; CI: Exact Clopper-Pearson Confidence Interval

[1]P-values are from Fisher's exact 2-tailed tests of differences between groups in immunologic responder rates.

Tables with similar format to Table 117:

Table 118: Serologic Responses to *S. flexneri* 2a LPS, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 119: Serologic Responses to *S. flexneri* 2a IpaB, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 120: Serologic Responses to *S. flexneri* 2a IpaC, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 121: Serologic Responses to *S. flexneri* 2a IpaD, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 122: Serologic Responses to *S. sonnei* Invaplex, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 127: ALS Responses to *S. flexneri* 2a Invaplex, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
ALS IgA								
Day 4	n	xx						x.xxxx
	Responder %	xx.x						
	95% CI	xx.x, xx.x						
Day 6	n							
	Responder %							
	95% CI							
Day 8	n							
	Responder %							
	95% CI							
ALS IgG								
Day 4	n							
	Responder %							
	95% CI							
Day 6	n							
	Responder %							
	95% CI							
Day 8	n							
	Responder %							
	95% CI							

ALS: antibody in lymphocyte supernatant; IgA: immunoglobulin A; IgG: immunoglobulin G; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; Responder defined as ≥4-fold increase in titer from baseline; CI: Exact Clopper-Pearson Confidence Interval

[1]P-values are from Fisher's exact 2-tailed tests of differences between groups in immunologic responder rates.

Tables with similar format to Table 127:

Table 128: ALS Responses to *S. flexneri* 2a LPS, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 129: ALS Responses to *S. flexneri* 2a IpaB, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 130: ALS Responses to *S. flexneri* 2a IpaC, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 131: ALS Responses to *S. flexneri* 2a IpaD, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 132: ALS Responses to *S. sonnei* Invaplex, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 133: ALS Responses to *S. sonnei* LPS, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 134: ALS Responses to *S. sonnei* IpaB, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 135: ALS Responses to *S. sonnei* IpaC, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 136: ALS Responses to *S. sonnei* IpaD, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 137: Fecal IgA Responses to *S. flexneri* 2a Invaplex, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
Day 4	n	xx						x.xxxx
	Responder %	xx.x						
	95% CI	xx.x, xx.x						
Day 8	n							
	Responder %							
	95% CI							
Day 15	n							
	Responder %							
	95% CI							
Day 29	n							
	Responder %							
	95% CI							

IgA: Immunoglobulin A; N: Number of subjects in the immunogenicity population; n: Number of subjects with data at the specified time point; Responder defined as ≥4-fold increase in titer from baseline; CI: Exact Clopper-Pearson Confidence Interval

[1]P-values are from Fisher's exact 2-tailed tests of differences between groups in immunologic responder rates.

Tables with similar format to Table 137:

Table 138: Fecal IgA Responses to *S. flexneri* 2a LPS, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 139: Fecal IgA Responses to *S. flexneri* 2a IpaB, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 140: Fecal IgA Responses to *S. flexneri* 2a IpaC, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 141: Fecal IgA Responses to *S. flexneri* 2a IpaD, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 147: Salivary IgA Responses to *S. flexneri* 2a Invaplex, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Time Point	Statistic	Group 1A (N=X)	Group 1B, Naïve (N=X)	Group 1B, Veteran (N=X)	Group 2A (N=X)	Group 2B, Naïve (N=X)	Group 2B, Veteran (N=X)	P-Value[1]
Day 2	n	xx						x.xxxx
	Responder %	xx.x						
	95% CI	xx.x, xx.x						
Day 4	n							
	Responder %							
	95% CI							
Day 6	n							
	Responder %							
	95% CI							
Day 8	n							
	Responder %							
	95% CI							
Day 15	n							
	Responder %							
	95% CI							
Day 29	n							
	Responder %							
	95% CI							
Day 57	n							
	Responder %							
	95% CI							

IgA: immunoglobulin A; N: number of subjects in the immunogenicity population; n: number of subjects with data at the specified time point; Responder defined as ≥4-fold increase in titer from baseline; CI: Exact Clopper-Pearson Confidence Interval

[1]P-values are from Fisher's exact 2-tailed tests of differences between groups in immunologic responder rates.

Tables with similar format to Table 147:

Table 148: Salivary IgA Responses to *S. flexneri* 2a LPS, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 149: Salivary IgA Responses to *S. flexneri* 2a IpaB, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 150: Salivary IgA Responses to *S. flexneri* 2a IpaC, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 151: Salivary IgA Responses to *S. flexneri* 2a IpaD, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 152: Salivary IgA Responses to *S. sonnei* Invaplex, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 153: Salivary IgA Responses to *S. sonnei* LPS, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 154: Salivary IgA Responses to *S. sonnei* IpaB, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 155: Salivary IgA Responses to *S. sonnei* IpaC, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

Table 156: Salivary IgA Responses to *S. sonnei* IpaD, Immunologic Responder Rates by Study Day and Study Group - Immunology Population

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