Statistical Analysis Plan

A randomized, double-blind, placebo-controlled trial assessing the efficacy of once-daily dosing of Travelan® in a controlled human infection model for ETEC

NCT 05933525

Clinical Protocol:	IMM-124E-2002
Investigational Product:	Travelan®
Reference Product：	Placebo
Indication:	Travelers' diarrhea
Phase：	2
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Term	Definition
AE	adverse event
ALS	antibodies from lymphocyte supernatant
CBC	complete blood count
CF	ETEC colonization factor
CFA	ETEC colonization factor antigen
CFA+BS	colonization factor antigen agar plates with bile salts
CFU	colony-forming units
cGMP	current good manufacturing practice
CHIM	controlled human infection model
CTCAE	Common terminology criteria for adverse events
CPC	Pharmaron Clinical Pharmacology Center
DDID	Directorate for DoD Infectious Diseases
ELISA	enzyme-linked immunosorbent assay
ETEC	enterotoxigenic *Escherichia coli*
HBC	hyperimmune bovine colostrum
IgG	immunoglobulin G
IP	investigational product
IRB	institutional review board
LAL	limulus amebocyte lysate
LMIC	low- and middle-income country
LPS	lipopolysaccharides
LT	heat-labile enterotoxin
MCB	master cell bank
MH	Mueller-Hinton agar
MOP	Manual of Procedures
NMRC	Naval Medical Research Command
ORI	Operationally Relevant Infections Department
ORS	oral rehydration solution
PBMC	peripheral blood mononuclear cells
PE	protective efficacy
PI	principal investigator
QA	quality assurance
SD	study day
SOP	Standard operating procedure
ST	heat-stable enterotoxin
TD	travelers' diarrhea

USAMRDC OHARO OHRO	US Army Medical Research and Development Command, Office of Human and Animal Research Oversite, Office of Human Research Oversight

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report data presentations for the clinical study report for Protocol IMM-124E-2002.

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

The primary objective of this clinical study is to assess the protective efficacy of a single daily dose (1,200 mg) of Travelan® against moderate-to-severe diarrhea following challenge with ETEC strain H10407. The primary efficacy outcome is prevention and/or reduction of moderate to severe diarrhea, defined as ≥4 loose/liquid stools or ≥401 grams of loose/liquid stool in any 24-hour period post-challenge.

1.1.2 Secondary Objectives

The secondary objectives of this clinical study are to assess the safety and tolerability of once-daily dosing with Travelan® (1,200 mg) and a variety of clinical endpoints to further evaluate the efficacy of Travelan®. Secondary efficacy endpoints are chosen to support the primary endpoint in determining the protective efficacy (PE) of Travelan®. They further quantify and qualify the degree to which a participant experiences diarrhea. Additional comparisons between the placebo and test article groups are outlined below:

- Presence of AEs during the study period
- Maximum 24-hour loose stool (Grades 3-5) output
- Total loose stool (Grades 3-5) output
- Percent of subjects with severe diarrhea
- Percent of subjects with diarrhea of any severity
- Percent of subjects with fever, nausea, vomiting, anorexia, or abdominal pain/cramps rated as moderate-to-severe
- Percent of subjects who indicate they would have reduced their daily activity if they had been vacationing or traveling for business because of their ETEC illness
- Time to diarrhea onset and diarrhea resolution
- Number of CFUs of the challenge strain per gram of stool at 48 hours post-challenge
- Percent of subjects requiring early antibiotic treatment
- Percent of subjects requiring IV fluids
- ETEC disease severity score where all adverse events will be assessed individually and graded

1.1.3 Supplementary Objectives

The supplementary objectives of this clinical study are to discount the possible effect of antibiotics. Supplementary efficacy endpoints are chosen to support the primary endpoint in determining the PE of Travelan® before taken antibiotic treatment on Day 6.

1.2 STUDY ENDPOINTS

1.2.1 Primary Endpoint

The primary efficacy endpoint of this study is the prevention and/or reduction of moderate to severe diarrhea, defined as ≥4 Grade 3-5 stools in any 24-hour period post-challenge or ≥401 grams of Grade 3-5 stools in any 24-hour period post-challenge.

Stool will be graded based on a standard stool grading scale as follows:

Grade 1 = Fully formed (normal)
Grade 2 = Soft (normal)
Grade 3 = Thick liquid (diarrheal)
Grade 4 = Opaque watery (diarrheal)
Grade 5 = Rice-water (diarrheal)

1.2.2 Secondary Endpoints

- Presence of Travelan®-associated AEs during the study period
- Maximum 24-hour loose stool (Grades 3-5) output
- Total loose stool (Grades 3-5) output
- Percent of subjects with severe diarrhea
- Percent of subjects with diarrhea of any severity
- Percent of subjects with fever, nausea, vomiting, anorexia, or abdominal pain/cramps rated as moderate-to-severe
- Percent of subjects who indicate they would have reduced their daily activity if they had been vacationing or traveling for business because of their ETEC illness
- Time to diarrhea onset and diarrhea resolution
- Number of CFUs of the challenge strain per gram of stool at 48 hours post-challenge
- Percent of subjects requiring early antibiotic treatment
- Percent of subjects requiring IV fluids
- ETEC disease severity score to grade the severity of all adverse events from adjudication

1.2.3 Supplementary Endpoints

- Presence of PE for a 5 day period post challenge
- Presence of AEs for a 5 day period post challenge

- Maximum 24-hour loose stool (Grades 3-5) output prior to antibiotic administration on Day 6
- Total loose stool (Grades 3-5) output prior to antibiotic administration on Day 6
- Percent of subjects with severe diarrhea prior to antibiotic administration on Day 6
- Percent of subjects with diarrhea of any severity prior to antibiotic administration on Day 6
- Percent of subjects with fever, nausea, vomiting, anorexia, or abdominal pain/cramps rated as moderate-to-severe prior to antibiotic administration on Day 6
- Time to diarrhea onset and diarrhea resolution prior to antibiotic administration on Day 6

1.3 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled study designed to investigate whether Travelan® protects adult volunteers from clinical disease upon challenge with ETEC strain H104017. Up to 60 subjects will be randomized to receive either the investigational product or a placebo followed by challenge with ETEC strain H10407.

Table 1. Description of Study Groups

Test Article	n	Oral Dose Amount (in milligrams IgG)
Travelan®	30	1,200 mg once daily dosing
Placebo	30	1,200 mg once daily dosing

The trial will consist of 1-3 screening visits, approximately 12 in-patient days, 2 out-patient follow-up visits, and a follow-up phone call at 6 months post challenge. Subjects will be admitted 3 days prior to challenge Study Day -3 (SD -3), receive Travelan® or placebo once daily starting 2 days prior to challenge (SD -2). The ETEC challenge H10407 will be administered on SD 1. Subjects will continue Travelan®/ placebo dosing until antibiotic treatment is initiated on SD 6 or sooner if criteria for early treatment are met.
Travelan® is given orally each volunteer will receive either Travelan® or placebo once daily (6 caplets per dose) starting at 8 am after an overnight fast followed by a light breakfast 15-30 minutes after dosing, for a period of 7 days (from SD-2 through to SD5) or until antibiotic treatment is initiated.

A high protein milk product called ProMilk 85 was commercially sourced and used as a placebo control in the study. The placebo was repackaged and labeled to mirror Travelan® and appears similar to Travelan®.

Upon admission to the inpatient unit, clinical monitoring will consist of daily medical assessments with adverse event (AE) determination, vital signs three times daily, examination and weighing of all stools, stool culture work-up for the challenge study strain (up to 3 times daily), and safety laboratory tests - CBC, chemistry, renal, and hepatic panels. Antibiotic treatment will be initiated on SD6 post challenge or according to criteria for early antibiotic treatment. Subjects will be discharged from the inpatient facility when they feel well enough (clinical symptoms are resolved or resolving), 2

consecutive stool samples culture negative for the challenge strain and at least two doses of antibiotic treatment have been taken. Routine discharge is scheduled for SD 8 - when most subjects are expected to meet the discharge criteria. Subjects may be discharged earlier than SD8 if they meet criteria. Subjects who do not meet the discharge criteria on SD8 will remain on the unit until the criteria have been met.

The duration of the active study period (e.g., start of screening through final subjects finishing the study) is approximately 9 months, encompassing up to 60 days of screening/enrollment, 6 weeks for the inpatient/outpatient phase when data and samples will be collected, and a 6 month follow up phone contact to see if subjects are well and to complete the follow up medical interview. Additional study activities outside of the active study portion will include 3 to 6 months for immunology assays, and 2 months for analysis and reporting.

1.3.1 Randomization and Blinding

Consenting, eligible participants will be randomized in a 1:1 ratio to receive either the test article Travelan® or placebo. Randomization may be stratified based on blood group based on the correlation between ABO typing and susceptibility to moderate to severe diarrhea following challenge with ETEC strain H10407. The randomization scheme will utilize block sizes of 4 in order to ensure comparable numbers of Travelan® and placebo recipients.

Participant randomization will be generated by Pharmaron Clinical Services based on the enrollment sequence in the treatment table; therefore, the randomization plan will also provide the maximum number of sequence numbers by site.

Subjects who fulfill all inclusion/exclusion criteria and are eligible to participate will be assigned the next sequential treatment number by the Principal Investigator. The treatment number corresponds to a given treatment assignment known to the study pharmacist but blinded to the subject, the PI, and the remaining members of the clinical research site and collaborators.

Sealed, code-break envelopes will be provided to the research pharmacist if a given subject has a serious adverse event that requires unblinding of treatment assignment.

2 STATISTICAL CONSIDERATIONS

2.1 SAMPLE SIZE DETERMINATION

Using a Fisher's exact test with a two-sided alpha=0.05 and an ETEC disease rate of approximately 70% in placebo recipients, a sample size of 30 subjects per study arm (Travelan® or placebo) yields an approximate 80% power to detect a significant difference in moderate-severe ETEC-attributable diarrhea in placebo and passive prophylaxis subjects when the efficacy of Travelan® is >70%.

2.2 GENERAL CONSIDRATIONS

All subjects who receive Travelan® or placebo, irrespective of the number of doses of Travelan® or receipt of the challenge, will be included in the safety analyses. The null hypothesis for this study is that the diarrhea rates will be the same in groups receiving the placebo and Travelan®. It is represented as the diarrhea rate for Travelan minus the diarrhea rate for placebo. For the purpose of the DSMB, Safety data presentations will be provided along with limited efficacy presentations when deemed appropriate.

Efficacy summaries will be presented as randomized. Should a subject receive the incorrect treatment, they will be included in the randomized treatment group. Safety summaries will be presented as treated. Should a subject receive the incorrect treatment from which they were randomized, they will be included in the treatment group for which they received.

Continuous data, such as laboratory values and vital signs, will be summarized using mean, SD, median, min, max. Categorical endpoints will be summarized using counts and percents. Due to the nature of the efficacy measurements, no data imputations will be utilized.

All programming will be performed using SAS Version 9.4 or a later release.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Frequency counts and percentages will be used in tabulation for categorical variables. Unless specified otherwise, the percentage calculation will not take the missing values into account.

Each summary table produced will have a corresponding subject listing.

No inferences on hypothesis testing will be done.

2.3 ANALYSIS SETS

Safety analysis set – these are subjects randomized into the study who receive either Travelan or placebo, irrespective of the number of doses of Travelan or receipt of the challenge. A randomized subject will be included in this set regardless of receiving any treatment or not.

Intent-to-treat analysis set – these are subjects randomized into the study, who received at least one dose of blinded investigational product and have been challenged. In addition, a post-challenge stool sample evaluation must be recorded.

2.4 POOLING OF CENTERS

Not applicable

2.5 MULTIPLE COMPARISONS/MULTIPLICITY

Not applicable.

3 DATA HANDLING CONVENTIONS

3.1 DERIVED AND TRANSFORMED DATA

3.1.1 Baseline Definition

Baseline is the last assessment prior to the first dose of study product, which occurs on Day -2.

3.1.2 Study Day

Study Day will be calculated from the challenge date, and will be used to show start/stop day of assessments and events. Subjects will be challenged with ETEC strain H10407. There is no Day 0. Reference start date (SD-2) is defined as the first day of study medication.

Study Day (SD) = (date of event – reference start date)

3.2 ANALYSIS VISIT WINDOWS

Assessments during the blinded phase will be daily up to discharge from the study.

Visit windows will be ± 1 day for SD8 and SD 9. SD 15 and 29 will have visit windows ± 2 days. The final follow-up visit at SD181 will be ± 30 days.

3.3 PREMATURE WITHDRAWAL AND MISSING DATA

For subjects who drop out, if a given subject drops out of the study or becomes ineligible before the ETEC H10407 challenge, they will be replaced on the study by a subject given the same treatment. If a subject is replaced at the discretion of the Investigator upon consultation with the Sponsor, then a replacement randomization number will be assigned. The replacement randomization number will correspond to the same treatment assignment as the replaced subject.

Subjects who do not have at least one post-challenge diarrhea (stool) data will not be included in the primary intent-to-treat efficacy analysis. No missing data imputation will be performed.

4 STATISTICAL ANALYSES

4.1 SUBJECT INFORMATION

4.1.1 Disposition of Subjects

The numbers of subjects who were randomized, and who entered and completed the study should be provided, as well as the reasons for discontinuation.

4.1.2 Demographics and Baseline Characteristics

Demographics characteristics (age, blood type, sex, ethnicity, weight, height and BMI) will be summarized by treatment group using descriptive statistics for continuous measurements and listed by subject. Age will be calculated as the integer of differences between the birth date and the informed consent date in years.

Any relevant baseline disease characteristics will be summarized by treatment and listed by subject.

4.1.3 Medical History

All medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or a later release.

Medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment, using counts and percentages.

Medical history will be listed by subject.

4.1.4 Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE) on 1st Jun 2016 or later using the international nonproprietary name (INN; also called ‘generic name’) and therapeutic use (Anatomical Therapeutic code; ATC).

Prior and concomitant medication will be summarized by ATC 2nd level and preferred name. These medications will be tabulated separately by treatment for:

1) Prior medication, i.e. medication taken exclusively prior to treatment (i.e. with stop date before date of 1st study product)

2) Concomitant medication, i.e. medication taken during the treatment period (i.e. medication that is not stopped before date of 1st study product and not started after the End-of-trial examination).

Concomitant medications will be listed by subject.

4.1.5 Treatment Compliance

Overall percentage treatment compliance for every subject will be calculated and summarized. Compliance will be calculated as

(the number of doses of investigational product consume/7 days of treatment))*100%

Subjects are dosed once daily (1,200 mg) for 7 days.

4.2 EFFICACY ANALYSES

In all efficacy analyses, comparisons will be made between Travelan and placebo using a t-test for continuous endpoints, and a chi-square test for categorical endpoints. Non-parametric methods will be incorporated if assumptions of normality are not met. Kruskal-Wallis test will be used for continuous data, Fisher's exact test will be used for categorical data.

4.2.1 Primary Endpoint

The primary endpoint (Estimand) for determination of protective efficacy (PE) is ETEC-induced moderate-severe diarrhea defined as ≥ Grade 3-5 stools in any 24 hour period post challenge days or ≥ 401grams of Grade 3-5 stools in any 24 hour period occurring during the post-challenge period; however, subjects will be monitored for additional GI and non-GI complaints daily. The number of subjects who encounter moderate to severe diarrhea will be recorded for the Travelan group and the placebo group. Data will be analyzed to determine the incidence of diarrhea among subjects in the placebo vs. the Travelan® group and summarized by cohorts.

An unblinded statistician will perform interim data analysis following Day 29 of the second cohort, release the primary and secondary endpoint data listed in section 1.2.2. Protective Efficacy is calculated below:

Protective Efficacy (Primary Estimand)

$$PE\ (\%) = \frac{\text{incidence}_I\ (\text{placebo}) - \text{incidence}_I\ (\text{Travelan®})}{\text{incidence}_I\ (\text{placebo})} \quad \textbf{X 100\%}$$

where incidence refers to the number of subjects with ETEC-induced moderate-severe diarrhea relative to total number of subjects in a particular treatment group. The difference in the proportions between the two treatment groups will be tested using a Fisher's exact test. The PE ratio will be estimated, along with an approximate 95% confidence interval estimated using a a standard normal distribution and will be calculated for both safety and ITT (intent-to-treat) analysis sets. A possible Per-Protocol analysis set will exclude subjects who miss more than one dose of study treatment (active or placebo) in the 24 hours prior to receipt of the challenge. Subjects who miss more than one dose of study treatment in the

72 hours following the challenge and who do not meet the primary outcome before missing their second dose will also be excluded. Descriptive summaries using the Per Protocol analysis set will be optional.

4.2.2 Secondary Endpoint

The following secondary efficacy endpoints will involve comparisons between Travelan and placebo post challenge. In those endpoints that are percentages, a chi-square test for equality of proportions will be performed, assuming the data follow a normal distribution. If the normal assumptions are violated, non-parametric techniques, such as Fisher's Exact test will be used. P-values will be presented only for descriptive purposes, due to the number of comparisons made. In addition, for outcomes defined as a time to an event, Kaplan-Meier estimates of the survival curve will be plotted for each treatment.

- The number and percent of AEs (pre/post challenge) during the study period will be compared between Travelan and placebo and summarized by cohorts.
- The maximum 24-hour loose stools (Grade 3-5) output (in grams) will be compared between Travelan and placebo and summarized by cohorts.
- The total number of loose stool (Grades 3-5) output will be compared between treatments and summarized by cohorts.
- The number and percent of subjects with severe diarrhea post challenge will be compared between treatments and summarized by cohorts. Severe diarrhea is defined as 6 or more loose-liquid stools in a 24 hour period or totaling > 800 grams in a 24 hour period.
- The number and percent of subjects with diarrhea (Grade 3-5) of any severity post challenge will be compared between treatments and summarized by cohorts.
- The number and percent of subjects with fever, nausea, vomiting, anorexia, or abdominal pain/cramps rated as moderate-to-severe (Grade 2 – 4) and each AE separately will be compared between treatments and summarized by cohorts.
- The number and percent of subjects who indicate they would have reduced their daily activity if they had been vacationing or traveling for business because of their ETEC illness.
- The time to diarrhea onset and diarrhea resolution will be analyzed using Kaplan-Meier techniques for estimation and summarized by cohorts. Subjects who do not experience diarrhea will be censored on the date of withdrawal from the study or Day 29. Diarrhea episode resolution will be

defined as the start day of a 48-hour window with no grade 3-5 stools.

- The number and percent of CFUs (colony forming units)of the challenge strain per gram of stool at 48 hours post-challenge will be compared between treatments.
- The number and percent of subjects requiring early antibiotic treatment will be compared between treatments and summarized by cohorts. Antibiotic treatment administration will be documented on the concomitant medication CRF.
- The number and percent of subjects requiring IV fluids will be compared between treatments. The administration of IV fluids will be documented on the concomitant medications CRF.
- ETEC disease severity score (Porter, et al., 2016) will be compared between treatments.

The Disease severity score is based on objective signs observed from a subject, subjective symptoms reported by a subject, and a diarrhea score based on maximum 24 hour loose stools, either volume or frequency of episodes. The following table describes these components in further detail.

Disease Severity Score determination

Parameter	**Outcome**		**Score**
Objective signs	>1 episode of vomiting/24 hrs OR any fever		2
	1 episode of vomiting AND no fever		1
	No vomiting AND fever		0
Subjective symptoms	Moderate-sever lightheadedness OR		2
	Severe: nausea, malaise, headache or abdominal cramps		2
	Mild lightheadedness OR		1
	Mild-moderate: nausea, malaise, headache or abdominal cramps		1
	No 'subjective symptoms'		0
Diarrhea score (maximum 24 hr loose stools [1]	>1000 ml	> 12 episodes	4
	>600 to ≤1000 ml	>7 to 12 episodes	3
	>400 to ≤600 ml	>4 to 7 episodes	2
	>0 to ≤400 ml	1 to 4 episodes	1
	No loose stools	No loose stools	0

[1] diarrhea score assigned by the highest score determined by either maximum 24-hour output volume or frequency.

For each subject this score will be calculated based on the daily stool samples (through day 9). Scores range from 0 (no disease) to a maximum of 8 (most severe disease).

4.2.2 Stool Grading summary

Stool grading will be recorded each study day through day 9, using the following scale (from Section 1.2.1):

Grade 1 = Fully formed (normal)
Grade 2 = Soft (normal)
Grade 3 = Thick liquid (diarrheal)
Grade 4 = Opaque watery (diarrheal)
Grade 5 = Rice-water (diarrheal)

Stool grading will be summarized using counts and percents for each study day and treatment.

4.2.3 Supplementary Endpoint

The analysis of supplementary endpoints will be same as primary and secondary endpoints. In addition, the supplementary endpoints will be summarized by treatment group and by cohorts (both cohorts, cohort 1 and cohort 2). The cut off date will be at 8am on day 6.

4.3 SAFETY ANALYSIS

4.3.1 Extent of Exposure

The amount of study drug taken by the subjects will be summarized by treatment group. This will be calculated by the number of dosages taken multiplied by 1,200 mg. These amounts will be summarized using descriptive statistics for continuous measurements.

In addition, the number of days on study drug will be summarized by treatment group.

A listing showing exposure data will also be provided.

4.3.2 Adverse Events

An Adverse Event is any undesired event recorded for a subject based on the clinical monitoring of daily medical assessments, upon admission to the inpatient unit. Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). AEs will be coded according to MedDRA version 24.1 or a later release. Treatment related Adverse Events are those events recorded prior to the challenge. AEs occurring on study days –2 to 1 will be assessed as to their relationship with Travelan®. AEs occurring after receipt of the ETEC challenge (day 1) will be assessed as to their relationship with the Travelan®, ETEC H10407 challenge strain, or the antibiotic or study procedure, if applicable.

AEs will be classified as either pre-challenge or post-challenge AEs, and can be additionally classified

as either Solicited AEs or Unsolicited AEs.

The following ETEC-associated AEs will be solicited daily during the challenge phase:
1. Abdominal cramping
2. Abdominal pain
3. Anorexia (poor appetite)
4. Arthralgias
5. Bloating
6. Chills
7. Constipation
8. Excessive flatulence
9. Generalized myalgia
10. Headache
11. Lightheadedness
12. Malaise
13. Nausea
14. Urgency
15. Vomiting

The following will be documented via clinical assessments during the inpatient challenge phase:
1. Diarrhea (via stool logs)
2. Hypovolemia
3. Fever (oral temperature > 100.4° F)

AE will be categorized and summarized as solicited and unsolicited type of adverse events by before and after challenge. Solicited adverse events are those events a subject is specifically asked to record. An overview of AEs summary table will be presented. The number and percentage of subjects who experience at least 1 occurrence of the given events within each of the following categories will be summarized:

- Subjects with at least one AE
- Subjects with at least one grade ≥3 AE
- Subjects with at least one solicited AE
- Subjects with at least one unsolicited AE
- Subjects with at least one serious AE
- Subjects with at least one AE leading to drug withdrawn
- Subjects with at least one AE leading to death

The number and percentage of subjects reporting at least one AE grouped by MedDRA system organ class and preferred term will be tabulated. The summary tables will be provided, as appropriate for:

- All AEs
- AEs by Preferred Term
- AEs by maximal severity
- AEs by relationship to study treatment
- Treatment related AEs
- Grade ≥3 AEs
- Grade ≥3 AEs by maximal severity
- Grade ≥3 AEs by relationship to study treatment
- Treatment related Grade ≥3 AEs
- Solicited AEs
- Solicited AEs by maximal severity
- Solicited AEs by relationship to study treatment
- Treatment related Solicited AEs
- Unsolicited AEs
- Unsolicited AEs by maximal severity
- Unsolicited AEs by relationship to study treatment
- Treatment related Unsolicited AEs
- Serious AEs
- Serious AEs by maximal severity
- Serious AEs by relationship to study treatment
- Treatment related Serious AEs
- AEs leading to drug withdrawn
- AEs leading Deaths

The tabulation of Adverse Events will be based on decreasing frequency within a preferred term for the Travelan treatment group. If no information for any of the above AEs (such as Serious AEs), no need to provide crrosponding tables.

4.3.3 Clinical Laboratory Tests

Laboratory variables will be grouped under “Hematology”, “Clinical Chemistry”, or “Urinalysis”.
Baseline for all laboratory analyses will be the values obtained at the last assessment prior to the first dose of study products.
Laboratory data will be listed for each subject, flagging those observations outside normal ranges.

4.3.4 Vital Signs and Physical Examination Finding

4.3.4.1 Vital Signs

Vital signs and their change from baseline will be tabulated with descriptive statistics at each post-baseline visit and final visit for each parameter. The “final visit” will include the assessments taken at

SD 29, Early Withdrawal visit, and unscheduled visits, and will report the latest value(s). Vital signs summarized include oral body temperature, systolic blood pressure, diastolic blood pressure, respiratory rate, and pulse rate.

All vital sign values will be listed per subject, and visit.

4.3.4.2 Physical Examination Findings

Physical Exam results will be summarized at each visit using counts and percents. For each system (General appearance, HEENT, Skin, etc.) the numbers of normal, abnormal, not clinically significant, and abnormal, clinically significant will be presented by treatment.

4.3.4.3 Electrocardiogram

Screening ECG parameters will be presented for each subject that was eventually randomized into the study. The following ECG parameters are collected and will be included in this listing: Heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval (QT interval corrected for heart rate using Bazett's correction [QTcB] and Fridericia's correction [QTcF]).

4.4 Immunology

Not applicable.

5 PLANNED ANALYSES

5.1 Interim Analysis

A planned interim analysis will be conducted after the initial cohort has completed the in-center portion of the study per protocol section 5.9. The objective of the interim analysis is to allow the DSMB to determine if the trial should continue based on safety.

5.2 Safety Data Review

As needed, an aggregated safety review will be conducted no less frequent than every 6 months. The objective is to assess for any new onset SAEs or AEs of special interest after challenge mandated by the FDA.

5.3 Topline Results presentation

Once all subjects complete Day 29, unblinded topline tables and listings will be delivered to Immuron personnel. These tables are 14.1.1, 14.1.3, 14.2.1.1.1, 14.2.1.2.1, 14.2.2.1.1, 14.2.2.2.1, 14.2.2.3.1, 14.2.2.4.1, 14.2.2.5.1, 14.2.2.6.1, 14.2.2.7.1, 14.2.2.8.1, 14.2.2.10.1, 14.2.2.11.1, 16.2.7.9 and 16.2.7.10 (please refer to mock shells).

6 SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

Add supplementary analysis to discount the possible effect of antibiotics. New section added in Section 1.1.3, Section 1.2.3 and Section 4.2.3.

7 PROGRAMMING SPECIFICATIONS

Programming specifications will be provided in the SAP shells document.

8 TABLES/LISTINGS/FIGURES TEMPLATES /SHELLS

Tables/listing/figures templates/shells is provided as a separate document.

9. REFERENCES

Wei, Q., Wang, P., Yin, P, Confidence interval estimation for vaccine efficacy against COVID-19. *Frontiers in Public Health* 10:848120.

Connor, P., et al., Diarrhoea during military deployment: current concepts and future directions. Curr Opin Infect Dis, 2012. 25(5): p. 546-54.