Note to File:

Statistical Analysis for the VAC 049 Abbreviated CSR

Study Title:
A Phase 1 Randomized, Double-Blinded, Placebo-Controlled, Dose-Escalation Study to Assess the Safety, Tolerability and Immunogenicity of Live Attenuated, Oral Shigella WRSS1 Vaccine in Bangladeshi Toddlers (12 to 24 months old)

Version 1.0

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Prepared and distributed by:

The Emmes Corporation

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Trial Number Code:	Protocol: VAC 049
Development Phase:	Phase I
Investigational Products:	Live attenuated *S. sonnei* WRSS1
Sponsor:	PATH Vaccine Solutions
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Clinical Trial Initiation Date:	23 February 2017
Clinical Trial Completion Date:	10 January 2018
Date of Clinical Study Report:	04 April 2018
Version of Clinical Study Report:	v 1.0

SIGNATURE PAGE

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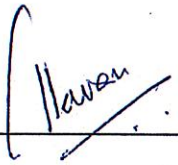
PROTOCOL NUMBER: VAC 049

PATH Medical Officer: Tushar Tewari, MD

Signed:  Date: 9/OCT/2018

The Emmes Corporation Statistician: Len Dally, MS

Signed:  Date: 9/OCT/2018

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List of Tables

1 Introduction

This is a note to file generated to provide a detailed summary of analysis conducted for VAC 049 abbreviated clinical study report. This was a single site, Phase 1, double-blind, randomized, placebo-controlled, dose-escalation study in toddlers (12-24 months old). The study was intended to enroll approximately 64 toddlers (12-24 months old) in 4 groups of 16, to receive three doses of $3x10^3$, $3x10^4$, $3x10^5$ or $3x10^6$ CFU WRSS1 vaccine or placebo (sterile saline solution). However, only the 16 participants in Cohort C1 ($3x10^3$ WRSS1(n=12) or placebo (n=4) with 3:1 randomization ratio) were enrolled and vaccinated as enrollment was terminated after Cohort C1 because the funder, the Bill and Melinda Gates Foundation (BMGF), made significant changes to the PATH Enteric Vaccine Initiative (EVI) portfolio and elected to discontinue support of the study, prior to enrollment of three higher-dose cohorts. Notification of study termination was sent to the FDA on October 4, 2017 as part of SN0015. As the study was terminated prematurely and prior to the development of a formal Statistical Analysis Plan (SAP), table shells were developed based on the statistical analysis sections in the study protocol, prior to completing the final analyses. In lieu of a full SAP, this note to file provides additional analysis details along with the previously-approved table shells for study documentation and archiving purposes.

2 Purpose of the Analysis

2.1 Primary Study Hypothesis

- Orally administered WRSS1 would be safe and tolerable in toddler recipients and would cause no major side effects in vaccinated participants.

2.2 Secondary Study Hypotheses

- WRSS1 was to generate a positive (4-fold rise in serum/plasma) immune response detectable in one or more assays in at least 50% of vaccinees.
- WRSS1 was to be able to replicate in the intestine as determined by fecal shedding.

3 Study Objectives

3.1 Primary Study Objective

- To evaluate the safety and clinical tolerance of WRSS1 in Bangladeshi toddlers (12-24 months old) by monitoring the occurrence and severity of clinical signs and symptoms after administration of three vaccine doses. All the analyses were to be performed by dose groups.

Safety was to be assessed by analyses of the following primary endpoints (events), where the unit of analysis in each case will be the proportion of participants with at least one event:

- any solicited reactogenicity
- any unsolicited AEs
- any SAEs
- unsolicited AEs and SAEs judged as having a reasonable possibility that the study product caused the event

3.2 Secondary Study Objectives

- To examine the immunogenicity of WRSS1.
- To assess the ability to replicate and duration of fecal shedding of WRSS1 following ingestion.

The secondary immunogenicity endpoints were chosen to further assess the mucosal and systemic immunogenicity. This was done by assessing:

- Frequency and magnitude of antigen specific serum IgG, IgA and IgM antibody titers to *S. sonnei* LPS, and *S. sonnei* Invaplex antigens after administration of one or three vaccine doses
- Frequency and magnitude of antigen-specific fecal IgA antibody titer to *S. sonnei* LPS and *S. sonnei* Invaplex antigens after administration of one or three vaccine doses
- Frequency and magnitude of antigen (LPS and Invaplex)-specific IgG, IgA, and IgM antibody titers in lymphocyte supernatant (ALS) to *S. sonnei* LPS and Invaplex antigens.

Finally, fecal shedding of vaccine was measured by the frequency and duration of detectable fecal presence of WRSS1 by culture and PCR.

3.3 Exploratory Objectives

To evaluate serum bactericidal activity and cytokine profile against WRSS1 in toddlers before and after vaccination.

4 Study Design

This was a single site, Phase 1, double-blind, randomized, placebo-controlled, dose-escalation study in toddlers (12-24 months old). The study was intended to enroll approximately 64 toddlers (12-24 months old) in 4 groups of 16, to receive three doses of $3x10^3$, $3x10^4$, $3x10^5$ or $3x10^6$ CFU WRSS1 vaccine or placebo (sterile saline solution). However, only the 16 participants in Cohort C1 ($3x10^3$ WRSS1(n=12) or placebo (n=4) with 3:1 randomization ratio) were enrolled and vaccinated as enrollment was terminated after Cohort C1 because the funder, the Bill and Melinda Gates Foundation (BMGF), made significant changes to the PATH Enteric Vaccine Initiative (EVI) portfolio and elected to discontinue support of the study, prior to enrollment of three higher-dose cohorts. Notification of study termination was sent to the FDA on October 4, 2017 as part of SN0015.

For full study details, please refer to Section 4 (Research Design and Methods) of the VAC 049 study protocol.

5 Study Procedures/Evaluations

Please refer to the following sub-sections from Sections 7 (Study Procedures/Evaluations), 8 (Study Schedule), and the Appendix I (Time and Event Schedule) of the VAC 049 study protocol:

- 7.1 Clinical Definitions
- 7.2 Concomitant Medication/Treatments
- 7.3 Laboratory Evaluations
- 8.1 Screening, Days -30 to -9 (Visit 01)
- 8.2 Day of First Vaccination (Visit 02)
- 8.3 Inpatient Period (Visit 03)
- 8.4 Discharge (Visit 03)
- 8.5 Outpatient Visits
- 8.6 Early Termination

6 Assessment of Safety

Please refer to the following sub-sections from Section 10 (Assessment of Safety) of the VAC 049 study protocol:

- 10.1.1 Adverse Event Definitions
- 10.1.2 Reactogenicity
- 10.1.3 Guidelines for Determine Causality of an Adverse Event
- 10.2 Safety Oversight – Data Safety Monitoring Board (DSMB)

7 Sample Size Calculation and Outcome Primary and Secondary Variables

7.1 Sample Size

Please refer to the following sub-sections from Section 12 (Sample size Calculation and Outcome Primary and Secondary Variables) of the VAC 049 study protocol:

- 12.1 Introduction
- 12.2 Sample Size

7.2 Final Data Analysis

Only Cohort C1 was enrolled and vaccinated, so all data analyses were limited to Cohort C1. All decisions about data analysis were made prior to database freeze and the final analyses were conducted after database freeze.

7.2.1 Analysis Populations

Safety Population: all enrolled participants who were randomized to either WRSS1 or Placebo and were vaccinated. This population was used in the analysis of all safety, study population, demographic & baseline characteristics data.

Per-Protocol Population*:* all randomized participants who received all three vaccinations and provided any immunology data through Day 84. This population was defined and interpreted based on the criteria in Section 12.3.2 of the study protocol, which stated that the analysis of

immunogenicity will include all participants who provide specimens through Day 84. This population was used in the analysis of all immunogenicity data.

The analysis populations were defined during blinded table shell preparation in collaboration between the sponsor and the CRO before final database lock and before breaking the blind.

7.2.2 General Analytic Plan

I. In this trial, only Cohort C1 was enrolled. Subjects were administered 3 doses of vaccine (3 X 10^3 CFU) or placebo, per randomized allocation, on Days 0, 28, and 56.

II. Shells for table, listing and figures are presented in Appendix I of this Note to File.

III. When the use of descriptive statistics to assess group characteristics was required, the following methods were to be used: for categorical variables, the number and percent in each category; for continuous variables, mean (with standard deviation), median, geometric mean and range (minimum, maximum).

IV. For statistical comparison between arms, the Chi-square test (if all expected frequencies in a table were >5) or Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables were to be utilized. The Clopper-Pearson exact two-sided 95% CI's were to be presented for within group proportion estimates, while the *t*-distribution was to be utilized to estimate the two-sided 95% CI's of within group estimates of geometric mean and between-group geometric mean fold-rise.

V. Demographic, baseline, and other study population data were to be summarized descriptively. These tables include participant disposition, analysis populations, demographic characteristics, medical history, abnormal physical examination and protocol deviations (Tables 7.1-7.6). Listings corresponding to the above descriptive summary tables were also to be generated.

VI. Due to the exploratory nature of the study, no adjustment was to be made for multiple testing. No imputation of missing data was to be performed as the complete samples among those in the analysis populations at each time point were to be analyzed.

VII. All analyses were to be unadjusted for potential covariates.

7.2.3 Safety Analysis

All visits after the participants had been exposed to the study product were to be included in the primary analysis of safety. To assess safety, the number and the percentages of participants experiencing at least one AE, and the number and percentage of participants experiencing each specific AE was to be tabulated according to maximum severity and relationship by study arm by both, overall and after each vaccination.

Analysis of safety data includes Tables 8.2.1 – 8.2.34, 8.3.1 – 8.5.1 Note that tables were numbered as Tables 9.2.1 – 9.2.34, 9.3.1 – 9.5.1 in CSR. The following describes the planned analysis for safety data:

- Descriptive summary and statistical comparison (WRSS1 vs Placebo) of solicited systemic reactogenicity
- Descriptive summary and statistical comparison (WRSS1 vs Placebo) of solicited intestinal reactogenicity
- Descriptive summary of unsolicited adverse event by MedDRA SOC and PT
- Listing of adverse events, serious adverse events, death (including narrative)
- Listing of Hematology and Biochemistry

7.2.4 Immunogenicity Analysis:

The magnitude of IgA, IgG and IgM ALS, and serum measures were to be evaluated on Days 0, 7, 35 and 63, while the magnitude of IgA fecal measures were to be evaluated on Days 0, 7, 28, 35, 56, 63, and 84. A fold rise response was to be defined as a 4-fold increase in titer value at a post-baseline visit when compared to the baseline visit (Day 0). The response rate was summarized for each post-baseline time point using the number and percent, and including two-sided 95% exact confidence intervals for the rate. Immune measures were to be measured against *S. sonnei* LPS and Invaplex antigens and hence, analyzed separately.

Analysis of immunology data includes Table 10.2.1 – 10.2.22. Note that tables were numbered as Tables 11.2.1 – 11.2.21 in the CSR and Table 10.2.22 was not produced since no data were available. The following describes the planned analysis for immunology data:

- Descriptive summary of IgA, IgG, and IgM in ALS and Serum
- Descriptive summary and statistical comparison (WRSS1 vs Placebo) of fold-rise from baseline, based on the ratio of follow-up to baseline titers, in IgA, IgG, and IgM in ALS and Serum
- Descriptive summary and statistical comparison (WRSS1 vs Placebo) of 4-fold rise, based on the ratio of follow-up to baseline titers, in IgA, IgG, and IgM in ALS and Serum.
- Descriptive summary of IgA, in Stool
- Descriptive summary and statistical comparison (WRSS1 vs Placebo) of fold-rise, based on the ratio of follow-up to baseline titers, from baseline in IgA in stool.
- Descriptive summary and statistical comparison (WRSS1 vs Placebo) of 4-fold rise, based on the ratio of follow-up to baseline titers in IgA in stool.
- Proportion of Participants with WRSS1 Shedding at any time after vaccination

8 References

1. Study Protocol: **PR16023_VAC 049_V4_14Feb2017**

2. Study CSR: **VAC049_Abbreviated-CSR_04Apr2018_v1.0**

9 Appendix I: Table Shells

Figure 1. CONSORT Diagram

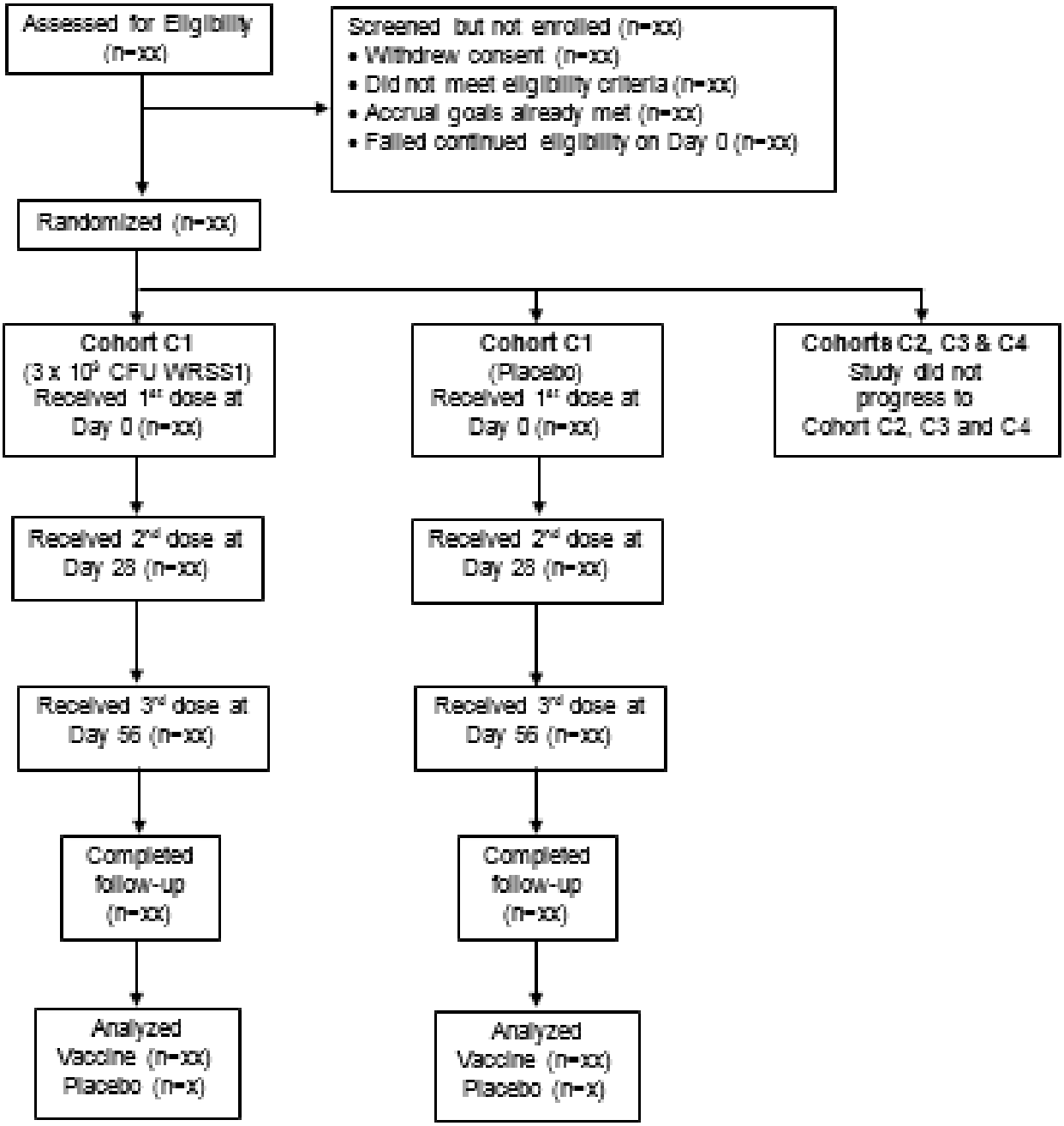

Table 7.1 Summary of Participant Disposition – All Participants

	Cohort C1		
	WRSS1 (3×10^3 CFU) (N=XX) n (%)	**Placebo (N=XX) n (%)**	**Total (N=XX) n (%)**
Screened	N/A	N/A	
Enrolled	N/A	N/A	
Randomized			
Participants completed the study			
Yes			
No			
If no, reason for premature termination			
Serious Adverse Event (other than death)			
Adverse Event, other than SAE			
Lost for Follow-up			
Non-Compliance/Protocol Deviation			
Voluntary Withdrawal by Participants/Parent			
Withdrawal by Investigator			
Termination of Site or Study by Sponsor			
Death			
Enrolled but not Vaccinated/Treated			
Others			

N= Number of participants screened and, n= Number of participants as per row description.

Denominator of the percentage is the number of randomized participants in the respective groups except for the 'Screened' and 'Enrolled' row.

N/A: Not Applicable.

Source: Listing 1. Listing of Participants Withdrawal

Table 7.2 Summary of Analysis Populations

	Cohort C1		
	WRSS1 (3×10^3 CFU) (N=XX) n (%)	**Placebo (N=XX) n (%)**	**Total (N=XX) n (%)**
Safety Population			
Per-Protocol Population			

N=Number of participants randomized and, n= is number of participants as per row description.

Percentages are calculated based on all screened participants while disposition details are calculated based on all randomized participants.

Table 7.3 Summary of Demographic Characteristics – Safety Population

	Cohort C1		
Characteristics	**WRSS1 (3×10^3 CFU) (N=XX)**	**Placebo (N=XX)**	**Total (N=XX)**
Gender, n (%)			
Female			
Male			
Age (Years)			
n			
Mean (STD)			
Median (Min, Max)			
Race, n (%)			
Black			
White			
Asian			
Height (cm)			
n			
Mean (STD)			
Median (Min, Max)			
Weight (Kg)			
n			
Mean (STD)			
Median (Min, Max)			

N= Number of participants in the Safety Population and, n= Number of participants with non-missing data.
Denominator of the percentage is the number of non-missing participants in Safety Population within the respective groups.
Source: Listing 2. Listing of Demographic and other Baseline Characteristics

Table 7.4 Summary of Medical History at Screening

	Cohort C1		
	WRSS1 (3×10^3 CFU) (N=XX) n (%)	**Placebo (N=XX) n (%)**	**Total (N=XX) n (%)**
HEENT			
HEENT-Head			
HEENT-Eyes			
HEENT-Ears			
HEENT-Nose			
HEENT-Throat/Mouth			
Cardiovascular			
Cardiovascular-Heart/Veins or Arteries			
Respiratory			
Gastrointestinal			
Gastrointestinal-Stomach			
Gastrointestinal-Intestines			
Hepatobiliary/Pancreas			
Liver/Pancreas			
Gall bladder			
Urologic			
Neurologic			

Autoimmune Disease			
Previous Vaccination			
No			
Yes			
Polio			
BCG			
Rotavirus			

Others			

N= Number of participants in the Safety Population; n= Number of participants as per row description.
Denominator of the percentage is the number of non-missing participants in Safety Population within the respective groups.
Source: Listing 3. Listing of Medical History

Table 7.5 Summary of Abnormal Physical Examination Results at Screening

	Cohort C1		
Area/System	**WRSS1 (3×10^3 CFU) (N=XX) n (%)**	**Placebo (N=X) n (%)**	**Total (N=X) n (%)**
HEENT			
Skin			
Cardiovascular (heart)			
Respiratory (lung)			
Abdomen			
Musculoskeletal			
Neurological			
Lymph Nodes			
Other			

N= Number of participants in the Safety Population and n= Number of participants as per row description.
Denominator of the percentage is the number of participants in Safety Population within the respective groups.
Source: Listing 4. Listing of Physical Examination Results

Table 7.6 Summary of Protocol Deviation

	Cohort C1		
	WRSS1 (3×10^3 CFU) (N=XX) n (%)	**Placebo (N=XX) n (%)**	**Total (N=XX) n (%)**
Participant is Protocol Deviation			
Yes			
No			
If Yes, reason for protocol deviation			
Participant illness			
Participants unable to comply			
Participant/ parent refusal			
Clinic Error			
Pharmacy Error			
Laboratory Error			
Investigator/Study Decision			
Others			
Deviation resulted in an AE			
Deviation resulted in participant termination of study follow up			
Deviation affects or potentially affect, product stability			
Deviation Category			
Eligibility/enrollment			
Product administration schedule			
Follow up visit schedule			
Protocol Procedure/assessment			
Protocol administration			
Blinding policy/procedure			
Deviation met IRB reporting requirements			

N= Number of participants in the Safety Population and n= Number of participants as per row description.
Denominator of the percentage is the number of participants in Safety Population within the respective groups.
Source: Listing 5. Listing of Protocol Deviations

Table 8.1 Summary of Participant Vaccinations

	Cohort C1		
Vaccination	**WRSS1 (3×10^3 CFU) (N=XX) n (%)**	**Placebo (N=X) n (%)**	**Total (N=X) n (%)**
Received Vaccination #1			
Received Vaccination #2			
Received Vaccination #3			
Received All Vaccinations			

N= Number of participants in the Safety Population and n= Number of participants as per row description.
Denominator of the percentage is the number of participants in Safety Population within the respective groups.
Source: Listing 6. Listing of Participant Vaccinations

Table 8.2.1 Maximum Severity of Any Systemic Reactogenicity by Vaccination in Cohort C1 - Safety Population

	Cohort C1				
	WRSS1 (3×10^3 CFU) (N=XX)		Placebo (N=X)		P-value (Vaccine vs Placebo)
	x/n (%)	95% CI	x/n (%)	95% CI	
Maximum Overall					
Mild					0.xxx[1]
Moderate					
Severe					
Potential Life Threatening					
Any Severity					0.xxx[2]
Post Vaccination 1					
Mild					0.xxx[1]
Moderate					
Severe					
Potential Life Threatening					
Any Severity					0.xxx[2]
Post Vaccination 2					
Mild					0.xxx[1]
Moderate					
Severe					
Potential Life Threatening					
Any Severity					0.xxx[2]
Post Vaccination 3					
Mild					0.xxx[1]
Moderate					
Severe					
Potential Life Threatening					
Any Severity					0.xxx[2]

N=Number of participants in the Safety Population.

Grades are based on maximum severity per participant.

[1]Chi-square or Fisher's exact 2-tailed test if conditions for chi-square test are not satisfied.

[2]Chi-square or Fisher's exact 1-tailed test of more events in the WRSS1 arms than in the placebo arm.

Cells show frequency (x) and percent of participants with events.

n = number of participants that received vaccination.

CI = Exact 95% Confidence Interval for the proportion.

For Fever: Mild: ≥100.4°F (38°C), Moderate: >101.1°F (38.5°C), Severe: >102.0°F (39°C), Potentially Life-Threatening>104.0°F (40°C)

Note: tables for any intestinal reactogenicity event and other individual reactogenicity events (8.2.2 - 8.2.15) will have similar shells.

Table 8.2.16 Systemic Reactogenicity of Grade 2 or Greater Severity by Day Post Any Vaccination in Cohort C1 - Safety Population

	Cohort C1			
	WRSS1 (3×10^3 CFU) (N=XX)		Placebo (N=X)	
	x/n (%)	95% CI	x/n (%)	95% CI
Maximum Overall				
Day 0				
Day 1				
Day 2				
Day 3				
Fever				
Day 0				
Day 1				
Day 2				
Day 3				
Decreased Appetite				
Day 0				
Day 1				
Day 2				
Day 3				
Irritability				
Day 0				
Day 1				
Day 2				
Day 3				
Decreased Activity				
Day 0				
Day 1				
Day 2				
Day 3				

N=Number of participants in the Safety Population.

Cells show frequency (x) and percent of participants with events. n represent number of participants that received vaccination.

CI = Exact 95% Confidence Interval for the proportion.

For Fever: Mild: ≥100.4°F (38°C), Moderate: >101.1°F (38.5°C), Severe: >102.0°F (39°C), Potentially Life-Threatening>104.0°F (40°C)

Table 8.2.17 Systemic Reactogenicity of Grade 2 or Greater Severity by Day Post Vaccination 1 in Cohort C1 - Safety Population

Table 8.2.18 Systemic Reactogenicity of Grade 2 or Greater Severity by Day Post Vaccination 2 in Cohort C1 - Safety Population

Table 8.2.19 Systemic Reactogenicity of Grade 2 or Greater Severity by Day Post Vaccination 3 in Cohort C1 - Safety Population

Table 8.2.20 Intestinal Reactogenicity of Grade 2 or Greater Severity by Day Post Any Vaccination in Cohort C1 - Safety Population

	Cohort C1			
	WRSS1 (3×10^3 CFU) (N=XX)		Placebo (N=X)	
	x/n (%)	95% CI	x/n (%)	95% CI
Maximum Overall				
Day 0				
Day 1				
Day 2				
Day 3				
Abdominal Pain				
Day 0				
Day 1				
Day 2				
Day 3				
Nausea				
Day 0				
Day 1				
Day 2				
Day 3				
Vomiting				
Day 0				
Day 1				
Day 2				
Day 3				
Loose Stool				
Day 0				
Day 1				
Day 2				
Day 3				
Diarrhoea				
Day 0				
Day 1				
Day 2				
Day 3				

Table 8.2.20 Intestinal Reactogenicity of Grade 2 or Greater Severity by Day Post Any Vaccination in Cohort C1 - Safety Population (continued)

	Cohort C1			
	WRSS1 (3×10^3 CFU) (N=XX)		Placebo (N=X)	
	x/n (%)	95% CI	x/n (%)	95% CI
Dysentery				
Day 0				
Day 1				
Day 2				
Day 3				
Bloating				
Day 0				
Day 1				
Day 2				
Day 3				
Excess Flatulence				
Day 0				
Day 1				
Day 2				
Day 3				
Constipation				
Day 0				
Day 1				
Day 2				
Day 3				

N=Number of participants in the Safety Population.

Cells show frequency (x) and percent of participants with events. n represent number of participants that received vaccination.

CI = Exact 95% Confidence Interval for the proportion.

Table 8.2.21 Intestinal Reactogenicity of Grade 2 or Greater by Day Post Vaccination 1 in Cohort C1 - Safety Population

Table 8.2.22 Intestinal Reactogenicity of Grade 2 or Greater by Day Post Vaccination 2 in Cohort C1 - Safety Population

Table 8.2.23 Intestinal Reactogenicity of Grade 2 or Greater by Day Post Vaccination 3 in Cohort C1 - Safety Population

Table 8.2.24 Maximum Severity per Participant of Unsolicited Adverse Events Occurring within 28 Days After Any Vaccination in Cohort C1, by MedDRA SOC and PT - Safety Population

	Cohort C1			
	WRSS1 (3×10^3 CFU) (N=XX)		Placebo (N=X)	
	x/n (%)	95% CI	x/n (%)	95% CI
Any SOC				
Any PT				
Mild				
Moderate				
Severe				
Potential Life Threatening				
Any Severity				
SOC: Specify				
Any PT				
Mild				
Moderate				
Severe				
Potential Life Threatening				
Any Severity				
SOC: Specify				
PT: Specify				
Mild				
Moderate				
Severe				
Potential Life Threatening				
Any Severity				

N=Number of participants in the Safety Population.

Cells show frequency (x) and percent of participants with events. n represent number of participants that received vaccination.

CI = Exact 95% Confidence Interval for the proportion.

Note: Table will be extended for other SOC and PT.

Table 8.2.25 Maximum Severity per Participant of Unsolicited Adverse Events Related to Study Product Occurring Within 28 Days After Any Vaccination in Cohort C1, by MedDRA SOC and PT - Safety Population

Table 8.2.26 Maximum Severity per Participant of Unsolicited Serious Adverse Events(SAE) Occurring Within 28 Days After Any Vaccination in Cohort C1, by MedDRA SOC and PT - Safety Population

Table 8.2.27 Maximum Severity per Participant of Unsolicited Serious Adverse Events(SAE) Related to Study Product Occurring Within 28 Days After Any Vaccination in Cohort C1, by MedDRA SOC and PT - Safety Population

Table 8.2.28 Maximum Severity per Participant of Unsolicited Adverse Events Occurring Within 28 Days After Vaccination 1 in Cohort C1, by MedDRA SOC and PT - Safety Population

Table 8.2.29 Maximum Severity per Participant of Unsolicited Adverse Events Occurring Within 28 Days After Vaccination 2 in Cohort C1, by MedDRA SOC and PT - Safety Population

Table 8.2.30 Maximum Severity per Participant of Unsolicited Adverse Events Occurring Within 28 Days After Vaccination 3 in Cohort C1, by MedDRA SOC and PT - Safety Population

Table 8.2.31 Maximum Severity per Participant of Unsolicited Adverse Events Related to Study Product Occurring Within 28 Days After Vaccination 1 in Cohort C1, by MedDRA SOC and PT - Safety Population

Table 8.2.32 Maximum Severity per Participant of Unsolicited Adverse Events Related to Study Product Occurring Within 28 Days After Vaccination 2 in Cohort C1, by MedDRA SOC and PT - Safety Population

Table 8.2.33 Maximum Severity per Participant of Unsolicited Adverse Events Related to Study Product Occurring Within 28 Days After Vaccination 3 in Cohort C1, by MedDRA SOC and PT - Safety Population

Table 8.2.34 Overall Incidence of Unsolicited Serious Adverse Events Within 28 Days After Vaccination, by Vaccination in Cohort C1 - Safety Population

	Cohort C1					
	WRSS1 (3×10^3 CFU) (N=XX)		Placebo (N=X)		Total (N=X)	
	x/n (%)	95% CI	x/n (%)	95% CI	x/n (%)	95% CI
Maximum Severity -After Any Vaccination						
Mild						
Moderate						
Severe						
Potential Life Threatening						
Any Severity						
Maximum Severity- After Vaccination 1						
Mild						
Moderate						
Severe						
Potential Life Threatening						
Maximum Severity- After Vaccination 2						
Mild						
Moderate						
Severe						
Potential Life Threatening						
Any Severity						
Maximum Severity- After Vaccination 3						
Mild						
Moderate						
Severe						
Potential Life Threatening						
Any Severity						

Severity is the maximum per participant over all unsolicited adverse events

N=Number of participants in the Safety Population.

Cells show frequency (x) and percent of participants with events. n represent number of participants that received vaccination.

CI = Exact 95% Confidence Interval for the proportion.

Table 8.3.1 Listing of Unsolicited Non-Serious Adverse Events of Grade 2 or Greater Severity in Participants in Cohort C1 - Safety Population

Adverse Event Description	Onset/ End Date	After which vaccination	Onset Day Post-Vaccination	Duration (days)	Severity	Action Taken	Outcome	Relationship to Study Product	MedDRA© System Organ Class	MedDRA© Preferred Term
Participant xxxx, WRSS1(3 x 10^3 CFU)										
EPIGASTRIC PAIN	07OCT13 - 08OCT13	1	43	2	Grade 2	Concomitant Medication	Recovered/ resolved without sequelae	No	Gastrointestinal disorders	Abdominal pain upper
Participant yyyy, Placebo										
Participant zzzz, WRSS1 (3 x 10^3 CFU)										
Participant kkkk, WRSS1 (3 x 10^3 CFU)										

Table 8.3.2 Listing of Unsolicited Serious Adverse Events in Participants in Cohort C1 - Safety Population

Table 8.4.1 Listing of all Hematology and Biochemistry Results in Participants in Cohort C1 with any Grade 2 or Greater Severity - Safety Population

Green=Outside the Reference Range, Yellow=Grade 1, Orange=Grade 2, Red=Grade 3, Purple=Grade 4

		HEMATOLOGY															BIOCHEMISTRY				
		WBC	Hemo globin	Plate lets	Neutrophils		Lymphocytes		Monocytes*		Eosinophils		Basophils*		ESR*	RBC*	Creat inine	AST	ALT (SGPT)	GGT	Total Bili rubin
Visit	Age (Years)	10^9/L	gm/dL	10^9/L	%	cells/ mm^3	%	cells/ mm^3	%	10^9/L	%	10^9/L	%	10^9/L	m/ 1^{st} hr	10^{12}/L	U/L	umol/ L	U/L		umol/ L
Participant 11012, WRSS1 (3 x 10^4 CFU)																					
Screen -ing																					
Day 7																					
Participant 11019, WRSS1 (3 x 10^5 CFU)																					
Screen -ing																					
Day 7																					
Participant 11042, WRSS1 (3 x 10^5 CFU)																					
Screen -ing																					
Day 7																					
Participant 11050, Placebo																					
Screen -ing																					
Day 7																					

Table 8.5.1 Listing of all Physical Examination and Vital Signs Values in Participants in Cohort C1 with Any Abnormality Findings - Safety Population

Yellow=Abnormal NCS, Red=Abnormal, CS

		Physical Examination									Vital Signs				
											Heart Rate	Respiratory Rate		Axillary Temperature	
Visit	Age (Years)	HEENT	Skin	Lymph Nodes	Respiratory (Lung)	Cardio-vascular (Heart)	Abdomen	Neurological	Musculo-skeletal System	Other	Beats/ minute	Breaths/ minute		°C	
Participant 11012, WRSS1 (3 x 10^4 CFU)															
Screening															
Day 7															
Day 28															
Day 35															
Day 56															
Day 63															
Day 84															
Participant 11019, WRSS1 (3 x 10^5 CFU)															
Screening															
Day 7															
Day 28															
Day 35															
Day 56															
Day 63															
Day 84															

Table 10.2.1 IgA Antibodies in ALS, Descriptive Statistics - Per Protocol Population

	Invaplex		LPS	
	Placebo (N=XX)	**WRSS1 $3x10^3$ (N=XX)**	**Placebo (N=XX)**	**WRSS1 $3x10^3$ (N=XX)**
Day 0				
n				
Mean (SD) Log titer				
GMT				
95% CI for GMT				
Median				
Range				
Day 7				
n				
Mean (SD) Log titer				
GMT				
95% CI for GMT				
Median				
Range				
Day 35				
n				
Mean (SD) Log titer				
GMT				
95% CI for GMT				
Median				
Range				
Day 63				
n				
Mean (SD) Log titer				
GMT				
95% CI for GMT				
Median				
Range				

N=Number of participants in the Per-Protocol Population and n=Number of participants with non-missing values.
SD = Standard Deviation. GMT = Geometric Mean titer.

Table 10.2.2 IgG Antibodies in ALS, Descriptive Statistics - Per Protocol Population

Table 10.2.3 IgM Antibodies in ALS, Descriptive Statistics - Per Protocol Population

Same as 10.2.1

Table 10.2.4 Fold-Rise from Baseline in IgA Antibodies in ALS – Per-Protocol Population

	Invaplex		LPS	
	Placebo (N=XX)	**WRSS1 $3x10^3$ (N=XX)**	**Placebo (N=XX)**	**WRSS1 $3x10^3$ (N=XX)**
Day 7				
n				
Mean (SD) Log titer				
GMT				
95% CI for GMT				
Median				
Range				
Ratio (95% CI)[1]				
Day 35				
n				
Mean (SD) Log titer				
GMT				
95% CI for GMT				
Median				
Range				
Ratio (95% CI)[1]				
Day 63				
n				
Mean (SD) Log titer				
GMT				
95% CI for GMT				
Median				
Range				
Ratio (95% CI)[1]				

N=Number of participants in the Per-Protocol Population and n=Number of participants with non-missing values

SD = Standard Deviation. GMT = Geometric Mean titer.

[1] WRSS1 versus Placebo ratio, back-transformed estimates from Student's Test of difference between mean Log Titers.

Table 10.2.5 Fold-Rise from Baseline in IgG Antibodies in ALS – Per-Protocol Population

Table 10.2.6 Fold-Rise from Baseline in IgM Antibodies in ALS – Per-Protocol Population

Same as 10.2.4

Table 10.2.7 4-Fold Rise[1] in IgA Antibodies in ALS Proportion of Participants with at Least a 4-Fold Rise from Baseline – Per-Protocol Population

	Invaplex		LPS	
	Placebo (N=XX)	**WRSS1 3x10^3 (N=XX)**	**Placebo (N=XX)**	**WRSS1 3x10^3 (N=XX)**
Day 7				
Number of observations				
n (%)				
95% CI				
P-Value[2]	0.xxxx		0.xxxx	
Day 35				
Number of observations				
n (%)				
95% CI				
P-Value[2]	0.xxxx		0.xxxx	
Day 63				
Number of observations				
n (%)				
95% CI				
P-Value[2]	0.xxxx		0.xxxx	
At Any Time				
Number of observations				
n (%)				
95% CI				
P-Value[2]	0.xxxx		0.xxxx	

N=Number of participants in the Per-Protocol Population and n=Number of participants with non-missing values

CI = Exact (Clopper-Pearson) Confidence Interval for the proportion.

[1] Fold rise is the ratio of follow-up titer/baseline titer. For those with a zero titer on Day 1, fold-rise was defined as the follow-up titer.

[2] Fisher's exact 2-tailed test of a difference in proportions between WRSS1 and Placebo.

Table 10.2.8 4-Fold Rise in IgG Antibodies in ALS Proportion of Participants with at Least a 4-Fold Rise from Baseline – Per-Protocol Population

Table 10.2.9 4-Fold Rise in IgM Antibodies in ALS Proportion of Participants with at Least a 4-Fold Rise from Baseline – Per-Protocol Population

Table 10.2.10 - Table 10.2.12 Replicate Table 10.2.1-10.2.3 for IgA, IgG and IgM Antibodies in Serum

Table 10.2.13 - Table 10.2.15 Replicate Table 10.2.4-10.2.6 for IgA, IgG and IgM Antibodies in Serum

Table 10.2.16 - Table 10.2.18 Replicate Table 10.2.7-10.2.9 for IgA, IgG and IgM Antibodies in Serum

Table 10.2.19 Replicate Table 10.2.1 for IgA Antibodies in Stool – Per Protocol Population, include extra visits (Days 28, 56 and 84)

Table 10.2.20 Replicate Table 10.2.4 for IgA Antibodies in Stool – Per Protocol Population, include extra visits (Days 28, 56 and 84)

Table 10.2.21 Replicate Table 10.2.7 for IgA Antibodies in Stool – Per Protocol Population, include extra visits (Days 28, 56 and 84)

Table 10.2.22 Proportion of Participants with WRSS1 Shedding at Any Time after Vaccination – Per-Protocol Population

	Placebo (N=XX)	**WRSS1 $3x10^3$ (N=XX)**
N. Obs.	x	xx
n (%)	x (xx.x)	x (xx.x)
95% CI	(0.xx – xx.x)	(0.xx – xx.x)

N=Number of participants in the Per-Protocol Population and n=Number of participants with non-missing values

N. Obs.= Number of observations

CI = exact confidence interval

Fisher's exact 2-tailed test of a difference in proportions between WRSS1 and Placebo: p=0.xxxx

Other Listings

1. Listing of Participants Withdrawn

2. Listing of Demographic and Other Baseline Characteristics

3. Listing of Medical History

4. Listing of Physical Examination Results

5. Listing of Protocol Deviations

6. Listing of Participant Vaccinations