

**Protocol C1091001**

**A PHASE 1/2, RANDOMIZED, PLACEBO-CONTROLLED, OBSERVER-BLINDED  
TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND  
IMMUNOGENICITY OF A MULTIVALENT GROUP B STREPTOCOCCUS  
VACCINE IN HEALTHY ADULTS 18 TO 49 YEARS OF AGE**

**Statistical Analysis Plan Amendment 1**

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## 1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C1091001 is based on the final protocol amendment 1 dated 08MAR2017.

**Table 1. Summary of Major Changes in SAP Amendments**

SAP Version	Change	Rationale
1.0	Not Applicable	Not Applicable
Amendment 1 1.0	<ul style="list-style-type: none"> <li>Derivation of Grade 4 LR/SE based on investigator's assessment</li> <li>Changed asymptotic method to exact for CI for risk difference in Tier-2 AE summary</li> <li>Added FDA toxicity grade criteria for Eosinophils</li> <li>Added LLOQ values for IgG CCI</li> <li>Removed all safety figures</li> <li>Revised immunogenicity analyses</li> <li>Timing of the 1-month safety and 1-month immunogenicity analyses</li> </ul>	Based on team comments on the CSR shells

## 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C1091001. A brief description of the study design and the study objectives are given below. Subsequent sections describe analysis populations and give the definitions of the safety and immunogenicity endpoints followed by details of statistical reporting. A list of tables, listings and figures, mock-up tables, listings and figures, and programming rules are prepared separately based on the methods described in this document. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

### 2.1. Study Objectives

#### 2.1.1. Primary Objective

- To describe the safety and tolerability of various formulations of GBS6 at 3 dose levels in healthy adults 18 to 49 years of age.

#### 2.1.2. Secondary Objective

- To describe the immunogenicity of various formulations of GBS6 at 3 dose levels for all vaccine serotypes (Ia, Ib, II, III, IV and V).

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## 2.2. Study Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of 3 ascending dose levels of GBS6 formulated with or without AlPO<sub>4</sub> administered in healthy adults aged 18 to 49 years.

Approximately 363 healthy adults aged 18 to 49 years of age will be randomized to receive a single dose of 1 of 3 dose levels of GBS6 formulated with or without AlPO<sub>4</sub> or placebo (saline control). This study will utilize a sentinel-cohort design CCI

. Refer to Table 2 for a detailed description of the number of subjects per group. Safety data through 14 days for subjects enrolled in each sentinel cohort will be reviewed and if deemed acceptable, enrollment of the expanded cohort will proceed at that same dose level.

Blood will be collected at screening and at the 1-week after vaccination follow-up visit for hematology and chemistry assessments in all subjects enrolled in each sentinel cohort.

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For all subjects, blood will also be collected immediately prior to study vaccination on Day 1, and 1 week, 2 weeks, 1 month, 3 months and 6 months after vaccination for immunogenicity assessment. Local reactions and systemic events will be collected for 14 days after vaccination. Adverse events (AEs) will be assessed up to 1 month after vaccination. Serious adverse events (SAEs) and medically attended adverse events (MAEs) will be assessed through 6 months after vaccination. In addition, AEs occurring up to 48 hours after the Visit 5 (3 months after vaccination) and Visit 6 (6 months after vaccination) blood draws that are related to study procedures will be collected.

An internal review committee (IRC) will review the 14-day safety data from each sentinel cohort prior to determining if expanded enrollment should begin at that dose level and whether enrollment in the sentinel cohort at the next highest dose should begin.

This study will utilize an external data monitoring committee (E-DMC) for regular review of accumulating safety data and for ad hoc review if a stopping rule is met, to provide a review of safety findings and the IRC recommendations.

**Table 2. Planned Subjects: Total and Number in Each Group**

Dose Level/Formulation Groups		Approximate Number of Subjects	
		CCI	TOTAL
<b>Lowest Dose Cohort</b>	GBS6 lowest dose (5 µg <sup>c</sup> ) with AlPO <sub>4</sub>		52
	GBS6 lowest dose (5 µg <sup>c</sup> ) without AlPO <sub>4</sub>		52
	Placebo (saline control)		17
<b>TOTAL</b>			121
<b>Middle Dose Cohort</b>	GBS6 middle dose (10 µg <sup>c</sup> ) with AlPO <sub>4</sub>		52
	GBS6 middle dose (10 µg <sup>c</sup> ) without AlPO <sub>4</sub>		52
	Placebo (saline control)		17
<b>TOTAL</b>			121
<b>Highest Dose Cohort</b>	GBS6 highest dose (20 µg <sup>c</sup> ) with AlPO <sub>4</sub>		52
	GBS6 highest dose (20 µg <sup>c</sup> ) without AlPO <sub>4</sub>		52
	Placebo (saline control)		17
<b>TOTAL</b>			121
<b>Study TOTAL</b>			363

Abbreviations: AlPO<sub>4</sub> = aluminum phosphate; CPS = capsular polysaccharide.

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### 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

#### 3.1. Primary Endpoints

- The proportion of sentinel-cohort subjects with clinical laboratory abnormalities following investigational product (IP) administration at the 1-week follow-up visit.
- The proportion of subjects reporting prompted local reactions within 14 days following IP administration (redness, swelling and pain at the injection site).
- The proportion of subjects reporting prompted systemic events within 14 days following IP administration (fever, nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain).
- The proportion of subjects reporting AEs within 1 month following IP administration.
- The proportion of subjects reporting MAEs and SAEs within 6 months following IP administration.



### 3.2. Secondary Endpoint

- GBS serotype-specific IgG geometric mean concentrations (GMCs) measured 1 month after vaccination.

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### 3.4. Baseline Variables

Day 1 is defined as the day of vaccination and start of the reporting period for local and systemic reactions in the e-diary.

#### Sentinel Cohort Subjects

Laboratory data will be collected for sentinel cohort subjects only. Data is collected during the screening visit, Visit 0 (-14 to -2 days prior to vaccination) and will be considered baseline data. For subjects with a rescreening visit, the rescreening laboratory results will be considered as the baseline data.



Day 1 is considered the baseline visit for the following assessments: Immunogenicity, [CCI] and vital signs.

#### Expanded Cohort Subjects

Day 1 is considered the baseline visit for the following assessments: Immunogenicity, [CCI] and vital signs.

#### **3.4.1. Demographic, Medical History and Baseline Characteristics**

Demographic variables collected include gender, race, ethnicity and date of birth. Age at time of vaccination (in years) will be derived based on birthday. For example, if the vaccination date is one day before the subject's 19th birthday, the subject is 18 years old.

Medical history of clinical significance will be collected and categorized according to the current version (at time of reporting) of the Medical Dictionary of Regulatory Activities (MedDRA).

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#### **3.6. Safety Endpoints**

##### **3.6.1. Adverse Events**

The time period for reporting AEs for all subjects is from the time the informed consent is signed to 1 month follow-up visit (Visit 4). For all subjects, only MAEs and SAEs will be collected at Visit 5 (3 month) and Visit 6 (6 month) follow-up visits. Additionally, AEs occurring up to 48 hours after Visit 5 (3 month) and Visit 6 (6 month) that are related to study procedure (e.g., blood draw) will be collected for all subjects.

All AEs are collected on the case report form (CRF) and will be categorized according to the current version (at time of reporting) of the Medical Dictionary of Regulatory Activities (MedDRA).

An immediate AE is defined as any AE that occurred within the first 30 minutes after IP (see Section 7.8.2 Immediate Adverse Events of the protocol).

A MAE is defined as a nonserious AE that results in an evaluation at a medical facility.

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AEs will be captured and reported in accordance with Pfizer reporting standards.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses may be performed for different tiers.

- Tier-1 events: These are prespecified events of clinical importance and, if any, are maintained in a list in the product's Safety Review Plan. There are no pre-identified tier-1 events for this study.
- Tier-2 events: These are events that are not tier-1 but are "common." A MedDRA preferred term (PT) is defined as a tier-2 event if there are 4 or more subjects in at least one vaccine group.
- Tier-3 events: These are events that are neither tier-1 nor tier-2 events.

### **3.6.2. Reactogenicity Data**

Reactogenicity data are solicited AEs collected using e-diary, during Days 1-14, starting on the day of the vaccination [Day 1 (Visit 1)] following the IP administration. The reactogenicity data will include local reactions (pain at injection site, erythema/redness, and induration/swelling), systemic events (fever, nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain) and the use of antipyretic medication. Clinical to provide any errors noted on e-diary and specific instructions on handling them.

#### **3.6.2.1. Local Reactions**

Local reactions reported in the e-diary are pain at injection site, erythema/redness, and induration/swelling.

##### Presence of Local Reactions (Proportion of Subjects Reporting)

The subject will record the presence or absence of pain at injection site in the e-diary as 'Mild', 'Moderate', 'Severe' or 'None'. The presence or absence of redness or swelling to be recorded as 'Yes' or 'No'. Additionally, if redness or swelling is present, then the subject will use a caliper to measure the largest diameter and record the measurement rounded up to the nearest whole number. Caliper units are converted to centimeters according to 1 caliper unit = 0.5 centimeters.

Only an investigator is able to classify a subject's local reaction as Grade 4, after physical examination of the subject or documentation from another medically qualified source (e.g., emergency room or hospital record), or, in the case of pain at the injection site only, telephone contact with the subject. If a subject experiences a Grade 4 local reaction, it will be captured in the unplanned visit CRF page. A severe local reaction entry in the e-diary that later is assessed as Grade 4 will be treated as Grade 4 for analyses.

The presence or absence of each local reaction on a given day is defined as follows:

= missing if value is missing on a given day;

= 'Yes', if the subject reports the reaction as 'Yes' for redness or swelling **or** 'Mild', 'Moderate' or 'Severe' or 'Grade 4' for pain at injection site on a given day;

= 'No' if the subject reports the reaction as 'No' for redness or swelling **or** 'None' for pain at injection site on a given day.

For each local reaction, the derivation of whether or not the specific reaction occurred on "any Day 1-14" will be made. The derivation of this variable is given in Table 3 below.

**Table 3. Derived Variables for Each Local Reaction**

Variable <sup>a</sup>	Yes (1)	No (0)	Missing (.)
Any Day 1-14	Subject reports the reaction as 'Yes' on any Day 1-14	Subject reports the reaction as 'No' on all 14 days or as a combination of 'No' and missing on all 14 days.	Subject reports the reaction as missing on all 14 days.

a. The variable will be defined for each of the 3 local reactions.

For any local reaction on any day, a similar definition can be applied as given in Table 4 below.

**Table 4. Derived Variables for Any Local Reaction**

Variable	Yes (1)	No (0)	Missing (.)
Any Day 1-14	Subject reports any local reaction as 'Yes' on any day during Days 1-14	Subject reports the reaction as 'No' on all 14 days or as a combination of 'No' and missing on all 14 days for all 3 local reactions.	Subject reports all of the local reactions as missing on all 14 days.

### Grading Scale for Local Reactions

The grading of local reactions is listed below in Table 5.

**Table 5. Local Reactions Grading Scale**

	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)<sup>a</sup></b>	<b>Grade 4<sup>b</sup></b>
<b>Pain at injection site</b>	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization
<b>Erythema/Redness</b>	2.5 cm to 5.0 cm (5 to 10 caliper units)	>5.0 cm to 10.0 cm (11 to 20 caliper units)	>10 cm (≥21 caliper units)	Necrosis or exfoliative dermatitis
<b>Induration/Swelling</b>	2.5 cm to 5.0 cm (5 to 10 caliper units)	>5.0 cm to 10.0 cm (11 to 20 caliper units)	>10 cm (≥21 caliper units)	Necrosis

- Subjects experiencing ≥ Grade 3 local reactions are to be seen by the study site.
- Grade 4 assessment should be made by the investigator; a Grade 4 event will not be collected in the e-diary but will be recorded as an AE on the CRF.
- Prevents daily activity, i.e., results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

### Maximum Severity for Local Reactions

The maximum severity (highest grading) of each local reaction within 14 days of vaccination will be derived. The maximum severity will be derived as follows:

= missing if values are missing for all Days 1-14;

= 0, if the subject reports all reactions as ‘No’ or a combination of missing and “No” for all Days 1-14;

= *highest grade* (maximum severity) within 14 days of vaccination, if the answer is not ‘No’ for at least 1 day.

### Duration of Each Local Reaction

The duration of each local reaction will be calculated in days as (resolution date of reaction - start date of reaction +1). Resolution of the event is the last day in which the event is recorded in the e-diary or the date the event ends if it is unresolved during the subject diary-recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing. Subjects with no reported reaction have no duration.

### Onset of Local Reaction

The onset day of each local reaction and any local reaction will be derived.

For the onset day of each local reaction, if subjects report severity change of the local reaction, the first day of initial reporting of that specific local reaction will be counted.

For the onset day of any local reaction, the first day of reporting any severity of any local reaction will be counted.

In summary, the following variables will be derived for local reaction:

1. Presence or absence of each local reaction on each day (Days 1-14) after vaccination.
2. Presence or absence of each local reaction on “any Day 1-14” after vaccination.
3. Maximum severity of each local reaction on “any Day 1-14” after vaccination.
4. Presence or absence of any local reaction on “any Day 1-14” after vaccination.
5. Duration of each local reaction after vaccination.
6. Onset day of each local reaction after vaccination.
7. Onset day of any local reaction after vaccination.

#### **3.6.2.2. Systemic Events**

Systemic events reported via e-diary are: fever, nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain. The highest temperature for each day for 14 days after vaccination to be recorded in the e-diary. The protocol defines fever as an oral temperature  $\geq 100.4^{\circ}\text{F}$  ( $38.0^{\circ}\text{C}$ ). For ongoing fever on Day 14, the stop date will be recorded in the CRF. Additionally, the subject to document the presence or absence of remaining systemic events in the e-diary as ‘Mild’, ‘Moderate’, ‘Severe’ or ‘None’. Subjects to be asked to assess severity of each event according to the [Table 6](#) below. Only an investigator is able to classify a subject’s systemic event as Grade 4, after physical examination of the subject or documentation from another medically qualified source (e.g., emergency room or hospital record), or telephone contact with the subject. If a subject experiences a Grade 4 systemic event, it will be captured under the unplanned visit CRF page. A severe systemic event entry in the e-diary that later is assessed as Grade 4 will be treated as Grade 4 for analyses.

Any temperature recorded as  $<95.0^{\circ}\text{F}$  ( $35.0^{\circ}\text{C}$ ) or  $>107.6^{\circ}\text{F}$  ( $42.0^{\circ}\text{C}$ ) will be treated as data entry errors and excluded from the analyses. For reporting purposes, fever will be analyzed using the following temperature ranges:

- $100.4^{\circ}\text{F}$  to  $101.1^{\circ}\text{F}$  ( $38.0^{\circ}\text{C}$  to  $38.4^{\circ}\text{C}$ )

- 101.2°F to 102.0°F (38.5°C to 38.9°C)
- 102.1°F to 104.0°F (39.0°C to 40.0°C)
- >104.0°F (>40.0°C)

**Table 6. Systemic Events Grading Scale**

	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)<sup>a</sup></b>	<b>Grade 4<sup>b</sup></b>
<b>Nausea/Vomiting</b>	No interference with activity or 1-2 times in 24 hours	Some interference with activity or >2 times in 24 hours	Prevents daily activity; requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
<b>Diarrhea</b>	2-3 loose stools in 24 hours	4-5 loose stools in 24 hours	≥6 loose stools in 24 hours	Emergency room visit or hospitalization
<b>Headache</b>	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization
<b>Fatigue/ Tiredness</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization
<b>Muscle pain</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization
<b>Joint pain</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization

Abbreviations: IV = intravenous.

- Subjects experiencing ≥ Grade 3 systemic events are to be seen by the study site.
- Grade 4 assessment should be made by the investigator; a Grade 4 event will not be collected in the e-diary but will be recorded as an AE on the CRF.
- Prevents daily routine activity, i.e., results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

The presence or absence of each systemic event on a given day is defined as follows:

= missing if value is missing on a given day;

= ‘Yes’, if the subject reports a temperature ≥38.0°C for fever **or** ‘Mild’, ‘Moderate’ or ‘Severe’ or ‘Grade 4’ for the remaining events on a given day;

= ‘No’ if the subject reports a temperature <38.0°C for fever **or** ‘None’ for the remaining events on a given day.

For each systemic event, the following variables will be derived:

1. Presence or absence of each systemic event on each day (up to Day 14) after vaccination.
2. Presence or absence of each systemic event on “any Day 1-14” after vaccination.
3. Maximum severity of each systemic event on “any Day 1-14” after vaccination.
4. Presence or absence of any systemic event on “any Day 1-14” after vaccination.
5. Duration of each systemic event after vaccination.
6. Onset day of each systemic event after vaccination.
7. Onset day of any systemic event after vaccination.

The derivation of these variables is similar to the derivation of the variables for local reactions ([Section 3.6.2.1](#)). Any systemic event includes fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain or joint pain.

### **3.6.2.3. Use of Antipyretic/Pain Medication**

The use and type of antipyretic and/or pain medication will be recorded in the e-diary for 14 days (Days 1-14) after vaccination.

The following variables will be derived similar to the derived variables for local reaction:

1. Use of antipyretic/pain medication on each day (Days 1-14) after vaccination.
2. Use of antipyretic/pain medication on “any Day 1-14” after vaccination.
3. Duration of use of antipyretic/pain medication after vaccination.
4. Onset day of antipyretic use after vaccination.

### **3.6.3. Laboratory Data**

Laboratory data will be collected from the sentinel cohort subjects at screening, at rescreening if applicable, and at Visit 2 (1-week follow-up visit). The parameters of interest at each visit are listed below in [Table 7](#).



**Table 7. Laboratory Tests**

Hematology	Chemistry
Hemoglobin	BUN and Creatinine
Hematocrit	AST, ALT
RBC count	Total bilirubin
Platelet count	Alkaline phosphatase
WBC count	
Total neutrophils (Abs)	
Eosinophils (Abs)	
Monocytes (Abs)	
Basophils (Abs)	
Lymphocytes (Abs)	

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = while blood cell.

The FDA toxicity grading scale in Table 8 below for healthy adult and adolescent volunteers enrolled in the preventive vaccine clinical trials will be adapted for use in grading laboratory test abnormalities.

**Table 8. Hematology and Blood Chemistry Toxicity Grading Scale**

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Male hemoglobin (Hb)	12.5-13.5 g/dL (125-135 g/L)	10.5-12.4 g/dL (105-124 g/L)	8.5-10.4 g/dL (85-104g/L)	<8.5 g/dL (<85 g/L)
Female hemoglobin (Hb)	11.0-12.0 g/dL (110-120 g/L)	9.5-10.9 g/dL (95-109g/L)	8.0-9.4 g/dL (80-94g/L)	<8.0 g/dL (<80 g/L)
Leukocyte increase (total WBCs <sup>a</sup> )	10.8-15.0 x 10 <sup>9</sup> /L (x10 <sup>3</sup> /μL)	>15.0-20.0 x 10 <sup>9</sup> /L (x10 <sup>3</sup> /μL)	>20.0-25.0 x 10 <sup>9</sup> /L (x10 <sup>3</sup> /μL)	>25.0 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)
Leukocyte decrease (total WBCs <sup>a</sup> )	2.5-3.5 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)	1.5-<2.5 x 10 <sup>9</sup> /L (x10 <sup>3</sup> /μL)	1.0-<1.5 x 10 <sup>9</sup> /L (x10 <sup>3</sup> /μL)	<1.0 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)
Neutrophil decrease (absolute neutrophil count)	1.5-2.0 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)	1.0-<1.5 x 10 <sup>9</sup> /L (x10 <sup>3</sup> /μL)	0.5-<1.0 x 10 <sup>9</sup> /L (x10 <sup>3</sup> /μL)	<0.5 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)
Platelets	125-140 x 10 <sup>9</sup> /L (x10 <sup>3</sup> /μL)	100-124 x 10 <sup>9</sup> /L (x10 <sup>3</sup> /μL)	25-99 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)	<25 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)
Eosinophils (Absolute)	0.65-1.5 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)	>1.5-5.0 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)	>5.0 x 10 <sup>9</sup> /L (x 10 <sup>3</sup> /μL)	Hypereosinophilic
Alanine aminotransferase (ALT <sup>b</sup> )	1.1-2.5 x ULN <sup>c</sup>	2.6-5.0 x ULN <sup>c</sup>	5.1-10.0 x ULN <sup>c</sup>	>10 x ULN <sup>c</sup>
Aspartate aminotransferase (AST <sup>d</sup> )	1.1-2.5 x ULN <sup>c</sup>	2.6-5.0 x ULN <sup>c</sup>	5.1-10.0 x ULN <sup>c</sup>	>10 x ULN <sup>c</sup>
Alkaline phosphatase	1.1-2.0 x ULN <sup>c</sup>	2.1-3.0 x ULN <sup>c</sup>	3.1-10 x ULN <sup>c</sup>	>10 x ULN <sup>c</sup>
Total bilirubin (in presence of ALT <sup>b</sup> or AST <sup>d</sup> abnormality)	1.1-1.25 x ULN <sup>c</sup>	1.26-1.5 x ULN <sup>c</sup>	1.51-1.75 x ULN <sup>c</sup>	> 1.75 x ULN <sup>c</sup>
Total bilirubin (in presence of normal ALT <sup>b</sup> and AST <sup>d</sup> )	1.1-1.5 x ULN <sup>c</sup>	1.6-2.0 x ULN <sup>c</sup>	2.0-3.0 x ULN <sup>c</sup>	> 3.0 x ULN <sup>c</sup>

**Table 8. Hematology and Blood Chemistry Toxicity Grading Scale**

	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Grade 4</b>
<b>Blood urea nitrogen (BUN)</b>	23-26 mg/dL	27 – 31 mg/dL	> 31 mg/dL	Requires dialysis
<b>Creatinine</b>	1.5-1.7 mg/dL	1.8-2.0 mg/dL	2.1-2.5 mg/dL	>2.5 mg/dL or requires dialysis

- a. WBC = white blood cell
- b. ALT = alanine aminotransferase
- c. ULN = upper limit of normal
- d. AST = aspartate aminotransferase

### 3.6.4. Physical Examinations, Including Vital Signs

Physical examination will be performed at screening visit (Visit 0) for sentinel subjects and prior to vaccination on Day 1 (Visit 1) for expanded cohort subjects. All physical exam results will be recorded as normal, abnormal or not done in the CRF.

Vital signs including weight, height, sitting systolic and diastolic blood pressure, pulse rate, respiratory rate and oral temperature will be measured at screening visit (Visit 0) for sentinel subjects only and prior to vaccination on Day 1 (Visit 1) for all subjects and recorded in the CRF.

## 3.7. Study Conduct

### 3.7.1. E-diary Completion

On a specific day, the subject is expected to complete all the questions [the 3 local reactions, the 7 systemic events (including fever), and the use of antipyretic medication] in e-diary. In that case, e-diary will be transmitted and considered as complete. The data could be missing in the e-diary for a specific day, in which case it will not be transmitted and considered incomplete. All the data reported on the e-diary will be transferred electronically to the e-diary vendor.

### 3.7.2. Nonstudy Vaccines and Concomitant Treatments

Any nonstudy vaccinations given from the signing of the informed consent to Visit 6 (Month 6) will be recorded in the CRF.

Any medications taken from the signing of the informed consent through Visit 4 (1 month after vaccination) will be recorded in the CRF. Additionally, any medication taken to treat AEs from the signing of the informed consent through Visit 6 (Month 6) will be recorded in the CRF.

Nonstudy vaccines and concomitant medications will be categorized according to the latest version (at time of reporting) of the World Health Organization (WHO) Drug Dictionary.

## 4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

### 4.1. Per Protocol Analysis Set

In this study, the per protocol analysis set will be referred to as the evaluable immunogenicity population. The evaluable immunogenicity population will be the primary population for all immunogenicity data analyses. The immunogenicity results will be summarized according to the vaccine group as administered, which by the population definition, is equivalent to the vaccine group as randomized.

The evaluable immunogenicity population will include subjects who:

- Are eligible (have signed informed consent and met all inclusion/exclusion criteria) and randomized into the study;
- Have received GBS6 or placebo as randomized;
- Have a Visit 4 (1 month after vaccination) blood drawn for assay testing within 27 to 45 days, inclusive, after vaccine administration;
- Have at least one valid and determinate assay result for the 1 month after vaccination visit;
- Has no major protocol violation as determined by the study clinician.

Major protocol violations will be determined by clinical review. A major protocol violation is a protocol violation that, in the opinion of the sponsor's global medical monitor would materially affect assessment of immunogenicity, e.g., subject receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's global medical monitor will identify those subjects with protocol violations before any immunogenicity analysis is carried out.

### 4.2. Full Analysis Set

In this study, the full analysis set will be referred to as modified intent-to-treat (mITT) population.

All randomized subjects who have at least one valid and determinate assay result will be included in the mITT population. The immunogenicity results based on mITT population will be summarized according to the vaccine group as randomized and be performed for key immunogenicity endpoint(s). For non-key endpoints, immunogenicity analyses based on the mITT population will be performed only if there is a sizable difference (e.g. ~ 10%) in the

number of subjects between the mITT and the evaluable immunogenicity populations. The key and non-key endpoints are listed below in Table 9.

**Table 9. Analysis Populations for Key and Non-Key Endpoints**

Endpoint	Analysis Based on Evaluable Immunogenicity Population	Analysis Based on mITT Population
<b>Key Immunogenicity Endpoint</b>		
GBS serotype-specific IgG GMCs measured 1 month after vaccination	Yes	Yes
<b>Non Key Immunogenicity Endpoint(s)</b>		
CCI		

### 4.3. Safety Analysis Set

In this study, the safety analysis set will be referred to as the safety population.

All subjects who received GBS6 vaccine or placebo injection will be included in the safety population. For the safety analyses, subjects will be analyzed according to the vaccine group as administered. The safety population is the analysis population for all the safety endpoints.

### 4.4. Other Analysis Sets

No other analysis sets will be defined in this study.

### 4.5. Treatment Misallocations

- Randomized but not vaccinated: these subjects will not be included in the safety population for safety analyses. These subjects will not be included in the evaluable

immunogenicity population, but they will be included in the mITT population for immunogenicity analyses for subjects with valid and determinant assay results. The immunogenicity results for these subjects will be reported under the vaccine group as randomized.

- Vaccinated but not randomized: these subjects will be included in the safety population for safety analyses and will be reported under the vaccine group based on the vaccine received. They will be excluded from immunogenicity analyses based on either evaluable immunogenicity or mITT populations.
- Randomized but received incorrect vaccine: these subjects will be included in the mITT population for immunogenicity analyses if any assay results are available and will be reported under the vaccine group based on the randomized vaccine group in the analysis. These subjects will also be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received. These subjects will be excluded from the evaluable immunogenicity population for immunogenicity analyses.

## 5. GENERAL METHODOLOGY AND CONVENTIONS

### 5.1. Hypotheses and Decision Rules

#### 5.1.1. Statistical Hypotheses

This is a Phase 1/2 First-In-Human (FIH) study to assess the safety, tolerability and immunogenicity of GBS6 vaccine administered with or without AlPO<sub>4</sub> or placebo. No formal statistical hypothesis testing will be performed. An estimation approach will be used to assess the safety and immunogenicity objectives.

#### 5.1.2. Statistical Decision Rules

Statistical decision rules will not be utilized in this study. All analyses are considered descriptive in nature.

### 5.2. General Methods

Descriptive summary statistics will be provided for all endpoints. Unless otherwise explicitly stated, descriptive statistics for continuous variables are: n, mean, median, standard deviation, minimum and maximum. Descriptive statistics for categorical variables are: the proportion (%), n (the numerator) and N (the denominator) used in the proportion calculation.

Unless otherwise explicitly stated, all safety and immunogenicity summaries will be presented for subjects from both sentinel and expanded cohorts combined, by dose/formulation level and vaccine group (hereafter referred to as vaccine group) as defined below:

1. GBS6 (5 µg)/AlPO<sub>4</sub>

2. GBS6 (5 µg)/no AlPO<sub>4</sub>
3. GBS6 (10 µg)/AlPO<sub>4</sub>
4. GBS6 (10 µg)/no AlPO<sub>4</sub>
5. GBS6 (20 µg)/AlPO<sub>4</sub>
6. GBS6 (20 µg)/no AlPO<sub>4</sub>
7. Placebo

### 5.2.1. Analyses for Binary Data

#### 5.2.1.1. Immunogenicity Data

For immunogenicity results, the 2-sided 95% confidence intervals (CIs) based on exact (Clopper and Pearson) method will be provided for each vaccine group and blood sampling timepoint by GBS6 serotype for the proportion of subjects achieving a defined value for IgG concentration as defined in [Section 3.6](#).

The exact CIs for a proportion will be computed using the F distribution. If  $r$  is the number of responses and  $n$  is the number of subjects, then it follows that  $p = r/n$  is the estimate of the proportion of responses. An exact 95% confidence interval can be computed by solving the following 2 equations. For the lower limit  $P_L$ , use

$$P_L = \frac{rF_L}{(rF_L + (n - r + 1))}$$

and for the upper limit  $P_U$ , use

$$P_U = \frac{(r + 1)F_U}{(n - r) + (r + 1)F_U}$$

where  $F_L$  is the quantile from the F distribution for  $\alpha=0.025$ , with numerator degrees of freedom equal to  $2r$  and denominator degrees of freedom equal to  $2(n-r+1)$ .  $F_U$  is the quantile from the F distribution for  $\alpha=0.975$ , with numerator degrees of freedom equal to  $2(r+1)$  and denominator degrees of freedom equal to  $2(n-r)$ . When  $r$  equals 0,  $F_L$  should be set equal to 1.0 so  $P_L$  equals 0. When  $r$  equals  $n$ ,  $F_U$  should be set equal to 1.0 so  $P_U$  equals 1.

The CI using the F distribution is described in Collett, (1991)<sup>1</sup>.

### 5.2.1.2. Safety Data

Similarly, the exact 2-sided 95% confidence intervals (CIs) using the Clopper and Pearson method will be provided by each vaccine group for all primary safety endpoints, proportions of subjects reporting local reactions, systemic events, AEs, SAEs, and MAEs.

For tier-2 AEs only, 95% CIs for the difference in proportions between each vaccine group and placebo based on the Chan and Zhang<sup>2</sup> method will be provided.

### 5.2.2. Analyses for Continuous Data

#### 5.2.2.1. Geometric Means (GMs)

The GBS6 serotype-specific IgG, CCI antibody levels at each blood sampling timepoint will be summarized by geometric means (GMCs or CCI) and the associated 2-sided 95% CIs by vaccine group. The GMCs CCI will be calculated as the mean of the logarithmically transformed assay results and back transformed to its original units. The 2-sided, 95% CIs will be constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results using Student's t distribution.

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#### 5.2.2.4. Reverse Cumulative Distribution Curves (RCDCs)

Empirical RCDCs will be presented graphically by plotting the proportion of subjects vs GBS6 antibody levels for each serotype separately by vaccine group and at 1 month after vaccination blood sampling timepoint. The RCDCs at other timepoints may be generated. The lower limit of quantitation (LLOQ) and/or defined threshold values will be marked on the horizontal axis.

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### 5.3. Methods to Manage Missing Data

#### 5.3.1. Immunogenicity Data

The LLOQ in  $\mu\text{g/mL}$  for each serotype of GBS IgG are set as follows: Ia, 0.0219; Ib, 0.0105; II, 0.0085; III, 0.0134; IV, 0.0045; V, 0.0745.

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The GBS6 IgG, CCI antibody levels above LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ or denoted as below limit of quantitation (BLQ) will be set to  $0.5 \times \text{LLOQ}$  for all analysis.

Values that are insufficient sera (QNS), indeterminate results, or recorded as “Not Done” will be set to missing. No imputation will be done for these missing values.



### 5.3.2. Safety Data

Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in the Safety Rulebook Summary.

#### 5.3.2.1. Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 14-day e-diary is available, the ‘any day 1-14’ data will be considered as non-missing.

The reactogenicity data are collected through e-diary, which does not allow subjects to skip the question. Therefore, for a specific day, as long as the e-diary data is transferred for that day, all of the reactogenicity data for the subject on that day is non-missing. No missing reactogenicity data will be imputed other than what is described in [Section 3.6.2](#).

## 6. ANALYSES AND SUMMARIES

### 6.1. Primary Endpoint(s)

#### 6.1.1. Proportion of Sentinel-Cohort Subjects With Clinical Laboratory Abnormalities Following IP Administration at the 1 Week Follow-Up Visit

##### 6.1.1.1. Primary Analysis

**Endpoint:** Abnormalities in safety laboratory parameters as measured by FDA Grade.

- Analysis timepoints: Visit 2 (1 week after vaccination).
- Analysis population: Safety population.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

#### Reporting results:

- Raw data: n and proportion will be presented for each FDA grade (1 thru 4) and laboratory parameters (Hemoglobin, Hematocrit ...) by vaccine group for sentinel cohort subjects only.

**Figures:** None

#### 6.1.2. Proportion of Subjects Reporting Prompted Local Reactions Within 14 Days Following IP Administration

##### 6.1.2.1. Primary Analysis

**Endpoints:** Maximum severity during the analysis time interval for pain at injection site, erythema/redness and induration/swelling.

- Analysis timepoints: Days 1-14.
- Analysis population: Safety population.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

**Reporting results:**

- Raw data: Numerator (n), denominator (N) used for the calculation of proportion, proportion and associated 2-sided exact 95% CI will be presented for each severity (mild, moderate, severe and Grade 4) of each local reaction by vaccine group.

**Figures:** None

**6.1.3. Proportion of Subjects Reporting Prompted Systemic Reactions Within 14 Days Following IP Administration****6.1.3.1. Primary Analysis**

**Endpoints:** Maximum severity during the analysis time interval for fever, nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain.

- Analysis timepoints: Days 1-14.
- Analysis population: Safety population.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

**Reporting results:**

- Raw data: Numerator (n), denominator (N) used for the calculation of proportion, proportion and associated 2-sided exact 95% CI will be presented for each severity (mild, moderate, severe and Grade 4) of each systemic event by vaccine group.

**Figures:** None

**6.1.4. Proportion of Subjects Reporting AEs Within 1 Month Following IP Administration****6.1.4.1. Primary Analysis**

**Endpoints:** Adverse events experienced by subjects.

- Analysis timepoints: Day 1 to 1 month after vaccination.

- Analysis population: Safety population.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

**Reporting results:**

- Raw data: Number of subjects with AEs (n), proportion and associated 2-sided exact 95% CI will be presented for any AE, each system organ class (SOC) and each preferred term within SOC by vaccine group.

**Figures:** None

**6.1.5. Proportion of Subjects Reporting MAEs and SAEs Within 6 months Following IP Administration**

**6.1.5.1. Primary Analysis**

**Endpoints:** MAEs and SAEs experienced by subjects.

- Analysis timepoints: Day 1 to 6 months after vaccination.
- Analysis population: Safety population.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

**Reporting results:**

- Raw data: Number of subjects with events (n), proportion and associated 2-sided exact 95% CI will be presented for any AE, each system organ class (SOC) and each preferred term within SOC by vaccine group.

**Figures:** None

**6.2. Secondary Endpoint(s)**

**6.2.1. GBS Serotype-Specific IgG GMCs Measured 1 Month After Vaccination**

**Endpoints:** GBS serotype-specific IgG antibody concentrations.

- Analysis timepoint: One (1) month after vaccination.
- Analysis population: Evaluable immunogenicity and mITT populations.
- Analysis methodology: Descriptive summary statistics & **CCI**.

- Supporting objective: Secondary objective.

**Reporting results:**

- Raw data: Number of subjects with valid assay data (N), GMCs and associated 2-sided 95% CI will be presented for each serotype by vaccine group.

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**Figures:** The following figures will be based on the evaluable immunogenicity population only.

- Empirical reverse cumulative distribution curves (RCDCs) for 1 month after vaccination timepoint will be generated separately for each serotype by vaccine group.

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## **6.6. Baseline and Other Summaries and Analyses**

### **6.6.1. Baseline Summaries**

Descriptive summary statistics for demographic characteristics (age at vaccination, gender, race and ethnicity) will be generated by vaccine group and the total sample based on safety population.



Subject data listings for demography and baseline characteristics data will also be listed.

#### **6.6.2. Study Conduct and Subject Disposition**

The number and proportion of randomized subjects will be included in the subject disposition summary. In addition, subjects who completed each follow-up visit, withdrew before the follow-up visit along with the reasons for withdrawal, will be tabulated by vaccine group. The reasons for withdrawal will be those as specified in the database. Additionally, subjects who missed at least one study procedure but continued in the study for safety follow-up will be summarized.

Subjects excluded from the evaluable immunogenicity and mITT populations will also be summarized with reasons for exclusion.

The number and proportion of subjects randomized, vaccinated and had blood drawn within the protocol-specified time frame, outside the specified window will be tabulated by vaccine group and the total sample.

The number and proportion of subjects with at least 1 medical history preferred term, arranged by system organ class will be tabulated for each vaccine group and the total sample. The medical history summary is based on the safety population.

The number and proportion of subjects with e-diary data not transmitted, transmitted by day (Days 1-14) and “All days” will be summarized by vaccine group and the total sample.

Subject data listings of subjects who withdrew during the study will be generated. Also, data listings for subjects excluded from evaluable and mITT populations will be generated separately.

The protocol deviations will be listed. In addition, subjects who do not receive the vaccine as randomized will be listed.

#### **6.6.3. Study Treatment Exposure**

Not applicable.

#### **6.6.4. Concomitant Medications and Non-Drug Treatments**

Nonstudy vaccines and medications taken after signing the informed consent and until the end of the study will be categorized according to the WHO Drug Dictionary and summarized in accordance with the sponsor reporting standards.

## 6.7. Safety Summaries and Analyses

### 6.7.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. CCI

Adverse events will be reported in accordance with the Pfizer reporting standards. For tier 2 and tier 3 events, the proportion of subjects with AEs in each vaccine group will be presented. In addition, for tier 2 AEs, 2-sided 95% CIs for the difference in observed proportions between each vaccine group and the placebo will be constructed. Tier 3 events will be summarized as part of the overall AE summary.

Listings of subjects reporting any AE and immediate AEs will be generated.

### 6.7.2. Reactogenicity Data

The derived endpoints ([Section 3.6.2](#)) for each local reaction, systemic event and use of antipyretic/pain medication will be summarized.

The number and percent of subjects with individual local reactions and any local reaction will be summarized on each of Days 1-14 separately. Two(2)-sided 95% CIs will also be displayed. A similar set of output may be produced combining reactions that are moderate or severe in grade. Similar analysis will be repeated for each systemic event and any systemic event.

For the maximum duration of local reactions, systemic events and use of antipyretic/pain medication, descriptive summary statistics will be provided separately.

For the onset (day) of local reactions, systemic events and use of antipyretic/pain medication, descriptive summary statistics will be provided separately.

The maximum reported diameters for redness and swelling will be summarized using descriptive statistics by vaccine group.

A subject data listing will be provided for all reactogenicity data and a listing for subjects experiencing severe redness or swelling.

### 6.7.3. Laboratory Data

Descriptive summaries for laboratory abnormalities at 1 week after vaccination visit will be provided by vaccine group. Also, a listing of laboratory data will be generated.

#### 6.7.4. Physical Examinations, Including Vital Signs

Descriptive summaries based on the safety population will be provided in accordance with the Pfizer reporting standards and listings may be generated.

### 7. INTERIM ANALYSES

#### 7.1. Introduction

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded study. Analyses results after each analysis described below will be provided to the appropriate sponsor personnel as needed to make program related decisions. In addition to these, unblinded safety data reviews by E-DMC to occur approximately twice a year. Additional details can be found in the E-DMC charter.

#### 7.2. Interim Analyses and Summaries

No formal interim analysis is planned for this study.

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### 8. REFERENCES

1. Collett D. *Modeling Binary Data*. London: Chapman & Hall; 1991.
2. Chan ISF and Zhang Z. Test based exact confidence intervals for the difference of two binomial proportions. *Biometrics*. 1999; 55:1201-1209.
3. Siddiqui O, Hung HM & O'Neill R: MMRM vs. LOCF: A Comprehensive Comparison Based on Simulation Study and 25 NDA Datasets, *Journal of Biopharmaceutical Statistics*, 2009, 19:2, 227-246.