Protocol C1091007

A PHASE 2, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A BOOSTER DOSE OF A GROUP B STREPTOCOCCUS 6-VALENT POLYSACCHARIDE CONJUGATE VACCINE (GBS6) IN HEALTHY ADULTS

Statistical Analysis Plan (SAP)

Version: 3

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 3/ 07 Aug 2020	Not applicable	Add IgG1 and IgM endpoints	1. Added LLOQ values for IgG1 and IgM (Section 5.3.3). 2. Added IgG1 GMCs before and 1 month after booster vaccination (Section 6.3.2). 3. Added IgM GMCs before and 1 month after booster vaccination (Section 6.3.3). 4. Added IgG1 GMFRs from before to 1 month after booster vaccination (Section 6.3.4). 5. Added IgM GMFRs from before to 1 month after booster vaccination (Section 6.3.5).
Version 2/ 26 Jun 2020	Not applicable	Add IgG levels of interest	1. Added proportion of participants achieving specific IgG concentration thresholds (Section 6.3.1). 2. Updated the serotype-specific baseline IgG levels of interest (Table 7).
Version 1/ 09 Apr 2020	Not applicable	Not applicable	Not applicable

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C1091007. This SAP Version 3 is based on the final protocol dated 07 Nov 2019. 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, Endpoints, and Estimands

2.1.1. Primary Objective

2.1.1.1. Primary Objective

- To describe the safety and tolerability of a single booster vaccination of group B streptococcus 6-valent polysaccharide conjugate vaccine (GBS6) in healthy adults.

2.1.2. Secondary Objectives

2.1.2.1. Secondary Objective: Overall

- To describe the immunogenicity for all vaccine serotypes after a single booster vaccination of GBS6.

2.1.2.2. Secondary Objective: By Baseline IgG GMCs

- To describe the immunogenicity for all vaccine serotypes after a single booster vaccination of GBS6 by baseline immunoglobulin G (IgG) geometric mean concentrations (GMCs) prior to the primary vaccination.

2.1.3. Primary Estimands

In participants receiving 1 dose of investigational product:

- The proportion of participants reporting prompted local reactions within 14 days following investigational product administration.

This estimand includes the following 4 attributes:

- Population: All participants who receive 1 dose of the investigational product and have safety data reported after receiving the investigational product.
- Variable: Presence/absence of prespecified local reactions within 14 days after vaccination.
- Intercurrent event(s): For participants who discontinue, all collected data will be included; missing data will not be imputed.
- Population-level summary: Proportion of participants reporting local reactions in each vaccine group.

  The dose/formulation levels (hereafter referred to as vaccine groups) in this study are defined as below:

  1. GBS6 (20 µg)/aluminum phosphate ($AlPO_4$), which is equivalent to 120 µg per 0.5-mL dose with $AlPO_4$.
  2. GBS6 (20 µg)/no $AlPO_4$, which is equivalent to 120 µg per 0.5-mL dose (no $AlPO_4$).

- The proportion of participants reporting prompted systemic events within 14 days following investigational product administration.

This estimand includes the following 4 attributes:

- Population: All participants who receive 1 dose of the investigational product and have safety data reported after receiving the investigational product.
- Variable: Presence/absence of prespecified systemic events within 14 days after vaccination.
- Intercurrent event(s): For participants who discontinue, all collected data will be included; missing data will not be imputed.
- Population-level summary: Proportion of participants reporting systemic events in each vaccine group.

- The proportion of participants reporting adverse events (AEs) through 1 month following investigational product administration.

This estimand includes the following 4 attributes:

- Population: All participants who receive 1 dose of the investigational product and have safety data reported after receiving the investigational product.
- Variable: Presence of AEs within 1 month after vaccination.
- Intercurrent event(s): For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in the safety rulebook.
- Population-level summary: Proportion of participants reporting AEs through 1 month after vaccination in each vaccine group.

- The proportion of participants reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) through 6 months following investigational product administration.

This estimand includes the following 4 attributes:

- Population: All participants who receive 1 dose of the investigational product and have safety data reported after receiving the investigational product.
- Variable: Presence/absence of MAEs and SAEs through 6 months after vaccination.
- Intercurrent event(s): For participants who discontinue, all collected data will be included; missing MAE and SAE dates will be imputed as described in the safety rulebook.
- Population-level summary: Proportion of participants reporting MAEs, and SAEs, throughout 6 months after vaccination in each vaccine group.

2.1.4. Secondary Estimands

In participants in compliance with the key protocol criteria (evaluable population):

- Group B streptococcus (GBS) serotype-specific IgG GMCs measured before and 1 month after booster vaccination.

This estimand includes the following 4 attributes:

  - Population: Evaluable immunogenicity analysis set as defined in Table 6.
  - Variable: Antibody concentrations before and 1 month after booster vaccination.
  - Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
  - Population-level summary: IgG GMCs.

- GBS serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) measured before and 1 month after booster vaccination.

This estimand includes the following 4 attributes:

  - Population: Evaluable immunogenicity analysis set as defined in Table 6.
  - Variable: Antibody titers before and 1 month after booster vaccination.
  - Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
  - Population-level summary: OPA GMTs.

- GBS serotype-specific IgG geometric mean fold rise (GMFR) from before to 1 month after booster vaccination.

This estimand includes the following 4 attributes:

  - Population: Evaluable immunogenicity analysis set as defined in Table 6.
  - Variable: Fold rise from before to 1 month after booster vaccination.
  - Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used.

Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.

- Population-level summary: GMFR from baseline for IgG concentrations.

- GBS serotype-specific OPA GMFR from before to 1 month after booster vaccination.

This estimand includes the following 4 attributes:

- Population: Evaluable immunogenicity analysis set as defined in Table 6.
- Variable: Fold rise from before to 1 month after booster vaccination.
- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
- Population-level summary: GMFR from baseline for OPA titers.

- GBS serotype-specific IgG GMCs measured 1 month after booster vaccination stratified by baseline prevaccination status (before the primary vaccination).

This estimand includes the following 4 attributes:

- Population: Evaluable immunogenicity analysis set as defined in Table 6.
- Variable: Antibody concentrations before and 1 month after booster vaccination.
- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
- Population-level summary: IgG GMCs by baseline serotype-specific colonization status, sex, age group, and serotype-specific IgG level(s), such as baseline IgG levels below or above the lower limit of quantitation (LLOQ) (see Section 6.4 for the details of baseline variables of interest).

2.2. Study Design

This will be a Phase 2, open-label study in healthy participants who received 1 of 6 dose/formulations of GBS6 at the US investigative sites in the C1091001 study. Participants who received placebo in the C1091001 study will not be eligible for study participation.

Healthy men and women will receive a single booster dose of GBS6 (20 µg) formulated with or without $AlPO_4$ based on the formulation received in the primary C1091001 study;

ie, participants who received 5 µg, 10 µg, or 20 µg without $AlPO_4$ in C1091001 will receive 20 µg without $AlPO_4$. Participants who received 5 µg, 10 µg, or 20 µg with $AlPO_4$ in C1091001 will receive 20 µg with $AlPO_4$.

Participants will have blood drawn prior to vaccination (Visit 1) and 1 month after vaccination (Visit 2) and will receive a 6-month safety follow-up telephone call (Visit 3). Electronic diaries (e-diaries) will be used to collect prompted local reaction and systemic event data for 14 days after vaccination (Days 1 through 14, where Day 1 is the day of vaccination), and AEs (including MAEs and SAEs) will be collected through Visit 2 and MAEs and SAEs through Visit 3.

An external data monitoring committee (E-DMC) will be utilized.

2.2.1. Approximate Duration of Participation of Each Participant

Study participation will be for approximately 6 months. The study duration will be approximately 1 year.

2.2.2. Approximate Number of Participants

Up to 297 participants previously enrolled in the C1091001 study received GBS6 and completed the study. This study will enroll all eligible participants who are willing to participate in this extension study.

2.2.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints (Safety)

- Prompted local reactions (redness, swelling, and pain at the injection site).
- Prompted systemic events (fever, nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain).
- AEs.
- MAEs and SAEs.

3.2. Secondary Endpoints (Immunogenicity)

- GBS serotype-specific IgG GMCs.
- GBS serotype-specific OPA GMTs.
- GBS serotype-specific IgG GMFRs.

- GBS serotype-specific OPA GMFRs.

[redacted]

3.4. Baseline Variables

Day 1 of booster vaccination is defined as the day of booster vaccination and the start of the reporting period for all endpoints. Day 1 of booster vaccination is considered as the baseline visit for primary safety endpoints and secondary immunogenicity endpoints as specified in Section 3.1 and Section 3.2. In addition, for the estimand "GBS serotype-specific IgG GMCs measured 1 month after booster vaccination stratified by baseline prevaccination status (before the primary vaccination)," baseline analyses will also include baseline prevaccination status, which is based on Day 1 of the primary vaccination.

3.5. Safety Endpoints

3.5.1. Reactogenicity Data

Reactogenicity data are collected using the participant's e-diary for local reactions and systemic events starting each evening for 14 days following vaccination (Day 1 through Day 14, where Day 1 is the day of vaccination). The investigator or designee must contact the participant in order to obtain stop dates for any reactions ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the case report form (CRF). Investigators are to provide any errors noted on the e-diary and specific instructions on handling them.

Missing e-diary data will not be imputed.

3.5.1.1. Local Reactions

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

Presence of Local Reactions (Proportion of Participants Reporting)

From Day 1 through Day 14, where Day 1 is the day of vaccination, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21 and >21), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 2. A participant with a severe (Grade 3 or above) local reaction will be prompted to contact the investigator to perform an unscheduled visit and assess the reaction.

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Grade 4[b]
Pain at injection site	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity[c]	Emergency room visit or hospitalization for severe pain at the injection site
Erythema/ redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis or exfoliative dermatitis
Induration/ swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis

a. Participants experiencing ≥ Grade 3 local reactions are to be seen by the study site. Refer to the Unscheduled Visits section of the protocol for further guidance.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the electronic diary but will be recorded as an AE on the case report form.
c. Prevents daily activity, ie, results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

Only an investigator is able to classify a participant's local reaction as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record), or, in the case of pain at the injection site only, telephone contact with the participant. If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor.

If a local reaction persists beyond the end of the e-diary period following vaccination, the participant will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

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 participant reports the reaction as "yes" for redness or swelling or "mild," "moderate," or "severe," or "Grade 4" for pain at the injection site on a given day;

= "No," if the participant reports the reaction as "no" for redness or swelling or "no" for pain at the injection site on a given day.

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

Table 3. Derived Variables for Any Local Reaction

Variable[a]	Yes (1)	No (0)	Missing (.)
Within 14 days	Participant reports the reaction as "yes" on any day (Days 1-14).	Participant reports the reaction as "no" on all 14 days or as a combination of "no" and missing on all 14 days.	Participant reports the reaction as missing on all 14 days.

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

Maximum Severity for Local Reactions

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

= Missing, if values are missing for all days (Days 1-14);

= 0, if the participant reports all reactions as "no" or a combination of missing and "no" for all days (Days 1-14);

= *Highest grade* (maximum severity) within 14 days after 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 on which the event is recorded in the e-diary or the date the event ends if it is unresolved during the participant 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. Participants with no reported reaction have no duration.

Onset of Local Reactions

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

For the onset day of each local reaction, if participants report a 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 (Days 1-14)" after vaccination.
3. Maximum severity of each local reaction on "any day (Days 1-14)" after vaccination.

4. Presence or absence of any local reaction on "any day (Days 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.

3.5.1.2. Systemic Events

From Day 1 through Day 14, where Day 1 is the day of vaccination, participants will be asked to assess nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the participant as "mild," "moderate," or "severe" according to the grading scale in Table 4. Participants will also be instructed to contact site staff if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for nausea/vomiting, diarrhea, headache, fatigue, muscle pain, or joint pain) within 14 days after vaccination. Study staff may also contact the participant to obtain additional information on Grade 3 events entered into the e-diary.

Only an investigator is able to classify a participant's systemic event as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. The procedure for notification of the sponsor is provided in the study documentation.

Further, if a systemic event persists beyond the end of the e-diary period following vaccination, the participant will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Fever is defined as an oral temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 14, temperature will be collected daily until the fever has resolved (1 day of temperature <100.4°F [38.0°C] in order to collect a stop date in the CRF). A participant with a fever >104.0°F (>40.0°C) will be prompted to contact the investigator to assess the fever and perform an unscheduled visit as appropriate. Study staff must also contact the participant to obtain additional information if a temperature of >102.0°F is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 5.

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 participant reports a temperature ≥100.4°F (38.0°C) for fever or "mild," "moderate," "severe," or Grade 4 for the remaining events on a given day;

= "No," if the participant reports a temperature <100.4°F (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 (Days 1-14) after vaccination.
2. Presence or absence of each systemic event on "any day (Days 1-14)" after vaccination.
3. Maximum severity of each systemic event on "any day (Days 1-14)" after vaccination.
4. Presence or absence of any systemic event on "any day (Days 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 3.5.1.1). "Any systemic event" includes fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, or joint pain.

Table 4. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Grade 4[b]
Nausea/vomiting	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
Diarrhea	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 for severe diarrhea
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity[c]	Emergency room visit or hospitalization for severe headache
Fatigue (= tiredness in diaries)	No interference with activity	Some interference with activity	Significant; prevents daily activity[c]	Emergency room visit or hospitalization for severe fatigue
Muscle pain	No interference with activity	Some interference with activity	Significant; prevents daily activity[c]	Emergency room visit or hospitalization for severe muscle pain

Table 4. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Grade 4[b]
Joint pain	No interference with activity	Some interference with activity	Significant; prevents daily activity[c]	Emergency room visit or hospitalization for severe joint pain

Abbreviation: IV = intravenous.

a. Participants experiencing ≥ Grade 3 systemic events are to be seen by the study site. Refer to the Unscheduled Visits section of the protocol for further guidance.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the electronic diary but will be collected as an AE on the case report form.
c. Prevents daily routine activity, ie, results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

Table 5. Ranges for Fever

100.4°F to 101.1°F (38.0°C to 38.4°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)

3.5.1.3. 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 reactions:

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

3.5.2. Adverse Events

All AEs, including nonserious AEs and SAEs, are collected on the CRF and will be categorized according to the current version (at the time of reporting) of the Medical Dictionary for Regulatory Activities (MedDRA). The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 2 (1 month after vaccination) for AEs and through and

including Visit 3 for MAEs and SAEs. AEs that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. Immediate AEs, defined as AEs occurring within the first 30 minutes after investigational product administration, will be assessed and documented in the AE CRF. The time of onset will be recorded for any AEs that occur on the same day as investigational product administration.

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

If an event is not an AE, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

AEs and SAEs will be captured and reported in accordance with Section 10.3.5 of the protocol.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.6.1).

Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's Safety Review Plan. There are no preidentified 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 participants in any vaccine group.

Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

3.5.3. Laboratory Data

3.5.3.1. Clinical Safety Laboratory Assessments

Not applicable.

3.5.3.2. Pregnancy Testing

Pregnancy tests will be performed in women of childbearing potential (WOCBP) on Day 1, immediately before administration of the vaccine dose. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy after administration of investigational product, the participant may remain in the study for blood sample collection and safety monitoring.

3.5.3.3. Vital Signs

Vital signs, including weight, height, sitting systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature, will be measured prior to vaccination on Day 1 (Visit 1) and recorded in the CRF.

3.5.3.4. Physical Examinations

Physical examination will be performed to evaluate any clinically significant abnormalities at the Day 1 visit. Results will be recorded as "normal," "abnormal," or "not done" in the CRF. Abnormal results must be recorded on source documents and the Physical Examination page of the CRF.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

For purposes of analysis, the populations are defined in Table 6:

Table 6. Analysis Sets (Populations for Analysis)

Population	Description
Enrolled	All participants who sign the informed consent document (ICD).
Evaluable immunogenicity	All participants who: • Are eligible (have signed informed consent and met all inclusion/exclusion criteria) and assigned to receive the investigational product in the study; • Have received 1 dose of GBS6 with or without $AlPO_4$ to which they were assigned; • Have a Visit 2 (1 month after vaccination) blood draw for assay testing within 27 to 45 days, inclusive, after vaccine administration; • Have at least 1 valid and determinate assay result at Visit 2 (1 month after vaccination); • Have no major protocol violation as determined by the study clinician. The evaluable immunogenicity population will be the primary population for all immunogenicity data analyses.
Modified intent-to-treat (mITT)	All participants who receive 1 dose of the investigational product and have at least 1 valid and determinate assay result after receiving the investigational product. Participants will be summarized according to the investigational product group to which they were assigned. The immunogenicity results based on the mITT population will be summarized for immunogenicity endpoints if there is a 10% or more difference between the mITT population and the evaluable immunogenicity population.
Safety	All participants who receive 1 dose of the investigational product and have at least 1 safety assessment after receiving the investigational product. Participants will be summarized according to the investigational product they received.

Major protocol violations will be determined by clinical review (through the data handling memo). A major protocol violation is a protocol violation that, in the opinion of the clinician, would materially affect assessment of immunogenicity (eg, participant 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 clinician will identify those participants with protocol violations before any immunogenicity analysis is carried out.

4.1. Treatment Misallocations

- Assigned but not vaccinated: This group includes participants who were assigned to a vaccine arm but not vaccinated. These participants will not be included in the safety population for safety analyses. These participants will not be included in the evaluable immunogenicity population, but they will be included in the mITT population for immunogenicity analyses for participants with valid and determinant assay results. The immunogenicity results for these participants will be reported under the vaccine group as assigned.

- Vaccinated but not assigned: This group includes participants who were vaccinated but not assigned to a vaccine arm. These participants will be included in the safety population for safety analyses and will be reported under the vaccine group based on the vaccine they received. They will be excluded from immunogenicity analyses based on either the evaluable immunogenicity population or the mITT population.

- Assigned but received incorrect vaccine: This group includes participants who were assigned to 1 vaccine arm but received an incorrect vaccine. These participants will be included in the mITT population for immunogenicity analyses if any assay result is available and will be reported under the vaccine group assigned in the analysis. These participants 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 participants 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

There are no formal statistical hypotheses for this study. 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 (%) and the n (the numerator) and N (the denominator) used in the calculation of the proportion.

All safety and immunogenicity summaries will be presented by vaccine group unless otherwise explicitly stated.

5.2.1. Analyses for Binary Endpoints

5.2.1.1. Safety Data

For safety data as defined in Section 3.5.1 and Section 3.5.2, the exact 2-sided 95% confidence intervals (CIs) using the Clopper and Pearson method[1] will be provided by vaccine group for all primary safety endpoints and for proportions of participants reporting local reactions, systemic events, AEs, SAEs, and MAEs.

For Tier 2 events, descriptive summary statistics (counts and percentages) will be provided for each vaccine group.

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 participants, then it follows that $p = r / n$ is the estimate of the proportion of responses. An exact 95% CI 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 α=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 α=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).[2]

5.2.1.2. GBS Prevaccination Status

The exact 2-sided 95% CIs using the Clopper and Pearson method will be provided by each vaccine group for the proportion of participants stratified by baseline GBS prevaccination status (before the primary dose) at relevant time points (see Section 6.4 for the list of baseline variables of interest).

5.2.2. Analyses for Continuous Endpoints

5.2.2.1. Geometric Means

The GBS6 serotype-specific IgG and OPA will be summarized by geometric means (GMCs or GMTs) and the associated 2-sided 95% CIs by vaccine group. The GMCs (GMTs) 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.

5.2.2.2. Geometric Mean Fold Rises

The fold rises in GBS6 serotype-specific antibody levels from before vaccination (Day 1) to each selected postvaccination time point for participants will be summarized, by vaccine group, via geometric means and associated 2-sided 95% CIs. The GMFRs are calculated as the mean of the difference of logarithmically transformed antibody levels after and before vaccination time points and back transformed to the original units. The associated 2-sided 95% CIs are also computed by back transformation of the CIs using Student's t distribution for the mean difference of measures on the logarithmically transformed assay results.

5.2.2.3. Reverse Cumulative Distribution Curves

Empirical reverse cumulative distribution curves (RCDCs) will be presented graphically by plotting the proportion of participants with the GBS6 serotype-specific antibody level equal to or exceeding the specified antibody level vs indicated antibody level for each serotype separately, by vaccine group, and at 1 month after vaccination for serotype-specific IgG concentration and OPA titers.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in the safety rulebook.

5.3.2. Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 14-day e-diary is available, the "any day (Days 1-14)" data will be considered as nonmissing.

The reactogenicity data are collected through e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day will be considered as nonmissing. No missing reactogenicity data will be imputed other than what is described in Section 3.5.1.

5.3.3. Immunogenicity Data

Values for sera 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.

In the first-in-human (FIH) study (C1091001), the LLOQ values in µg/mL for each serotype of GBS IgG are set as follows: Ia, 0.008; Ib, 0.011; II, 0.009; III, 0.010; IV, 0.005; V, 0.075.

In both FIH and C1091007 studies, the LLOQ values in titer for each serotype of GBS OPA are set as follows: Ia, 126; Ib, 150; II, 363; III, 130; IV, 224; V, 125.

In the C1091007 study, the LLOQ values in µg/mL for each serotype of GBS IgG are set as follows: Ia, 0.004; Ib, 0.010; II, 0.015; III, 0.012; IV, 0.006; V, 0.043.

The GBS6 IgG and OPA levels above LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ or denoted as below the limit of quantitation (BLQ) will be set to 0.5 × LLOQ for all analyses.

LLOQ values for the GBS IgG1 and IgM will be updated when they become available.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Prompted Local Reactions (Redness, Swelling, and Pain at the Injection Site) Within 14 Days After Vaccination

- Analysis set: Safety (Section 4).
- Analysis time points: Days 1 through 14. Refer to Section 3.5.1.1 for maximum severity.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; intermediate missing values will not be imputed.
- For each group, the numerator (n) and denominator (N) used for the calculation of proportion, proportion, and associated 2-sided exact 95% CI will be presented, by vaccine group, for the following variables:

- Presence or absence of each local reaction on each day (Days 1-14) after vaccination.
- Presence or absence of each local reaction on "any day (Days 1-14)" after vaccination.
- Presence or absence of any local reaction on "any day (Days 1-14)" after vaccination.
- Maximum severity of each local reaction on "any day (Days 1-14)" after vaccination.

- For each group, the n, mean, median, minimum, and maximum will be presented by vaccine group for the following variables:
  - Duration of each local reaction after vaccination.
  - Onset day of each local reaction after vaccination.
  - Onset day of any local reaction after vaccination.

Figures: None

6.1.2. Prompted Systemic Events (Fever, Nausea/Vomiting, Diarrhea, Headache, Fatigue, Muscle Pain, and Joint Pain) Within 14 Days After Vaccination

- Analysis population: Safety (Section 4).
- Analysis time points: Days 1 through 14.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; intermediate missing values will not be imputed.
- For each group, the numerator (n) and denominator (N) used for the calculation of proportion, proportion, and associated 2-sided exact 95% CI will be presented by vaccine group for the following variables:
  - Presence or absence of systemic event on each day (Days 1-14) after vaccination.
  - Presence or absence of each systemic event on "any day (Days 1-14)" after vaccination.
  - Presence or absence of any systemic event on "any day (Days 1-14)" after vaccination.
  - Maximum severity of each systemic event on "any day (Days 1-14)" after vaccination.

- For each group, the n, mean, median, minimum, and maximum will be presented by vaccine group for the following variables:
  - Duration of each systemic event after vaccination.
  - Onset day of each systemic event after vaccination.
  - Onset day of any systemic event after vaccination.

6.1.3. AEs Through 1 Month After Vaccination

- Analysis population: Safety (Section 4).
- Analysis time points: Day 1 through 1 month after vaccination.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in the safety rulebook.
- For each group, the number of participants with AEs within 1 month (30 days) (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, each system organ class (SOC), and each PT within each SOC, by vaccine group. For AEs classified as Tier 2, the number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for each vaccine group.

6.1.4. MAEs and SAEs Through 6 Months After Vaccination

- Analysis population: Safety (Section 4).
- Analysis time points: Day 1 through Month 6 after vaccination.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.
- For each group, the number of participants with AEs within 6 months (n), proportion, and associated 2-sided exact 95% CI will be presented for any MAEs and SAEs, each SOC, and each PT within each SOC, by vaccine group.

6.2. Secondary Endpoints

6.2.1. GBS Serotype-Specific IgG GMCs Before and 1 Month After Booster Vaccination

- Analysis population: Evaluable immunogenicity and mITT (provided there is a 10% or more difference with evaluable) populations (Section 4).

- Analysis time point: Before and 1 month after vaccination.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.
- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
- GMC of the IgG at each available time point for each serotype will be presented by vaccine group. For each vaccine group, the number of participants with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented.
- Figures of empirical RCDCs for 1 month after the vaccination time point will be generated separately for each serotype by vaccine group. The figures will be based on the evaluable immunogenicity population only.

6.2.2. GBS Serotype-Specific OPA GMTs Before and 1 Month After Booster Vaccination

- Analysis population: Evaluable immunogenicity and mITT (provided there is a 10% or more difference with evaluable) populations (Section 4).
- Analysis time point: Before and 1 month after vaccination.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.
- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
- GMT of the OPA at each available time point for each serotype will be presented by vaccine group. For each vaccine group, the number of participants with valid assay data (n), GMTs, and associated 2-sided 95% CI will be presented.
- Figures of RCDCs for 1 month after the vaccination time point will be generated separately for each serotype by vaccine group. The figures will be based on the evaluable immunogenicity population only.

6.2.3. GBS Serotype-Specific IgG GMFRs From Before to 1 Month After Booster Vaccination

- Analysis population: Evaluable immunogenicity population (Section 4).
- Analysis time points: Day 1 and 1 month after booster vaccination.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.
- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
- The number of participants with valid assay data (n), GMFRs of IgG, and associated 2-sided 95% CIs will be presented for each serotype by vaccine group.

6.2.4. GBS Serotype-Specific OPA GMFRs From Before to 1 Month After Booster Vaccination

- Analysis population: Evaluable immunogenicity population (Section 4).
- Analysis time points: Day 1 and 1 month after booster vaccination.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.
- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
- The number of participants with valid assay data (n), GMFRs of OPA, and associated 2-sided 95% CIs will be presented for each serotype by vaccine group.

6.2.5. GBS Serotype-Specific IgG GMCs Measured 1 Month After Booster Vaccination Stratified by Baseline GBS Prevaccination Status (Before the Primary Vaccination)

- Analysis population: Evaluable immunogenicity and mITT (provided there is a 10% or more difference with evaluable) populations (Section 4).
- Analysis time point: Before and 1 month after booster vaccination.
- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Secondary objective.
- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
- GMC of the IgG at each available time point for each serotype by baseline GBS prevaccination status will be presented by vaccine group. For each vaccine group, the number of participants with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented.

For details of baseline GBS prevaccination status and other baseline variables of interest, refer to Section 6.4.

6.3. Other Endpoint(s)

6.3.1. GBS Serotype-Specific IgG Concentrations ≥ C µg/mL

Analysis of the proportion of participants achieving serotype-specific IgG concentration thresholds (C) of 0.5 and 1.0 µg/mL will be performed.

- Analysis population: Evaluable immunogenicity.
- Analysis time point: Before and 1 month after booster vaccination.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Other objective.
- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
- The numerator (n), denominator (N) used for the proportion, proportion and associated 2-sided exact 95% CI will be presented for each analysis time point and serotype by vaccine group.

6.3.2. GBS Serotype-Specific IgG1 GMCs Before and 1 Month After Booster Vaccination

- Analysis population: Evaluable immunogenicity and mITT (provided there is a 10% or more difference with evaluable) populations (Section 4).
- Analysis time point: Before and 1 month after booster vaccination.
- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Secondary objective.

- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.

- GMC of the IgG1 at each available time point for each serotype will be presented by vaccine group. For each vaccine group, the number of participants with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented.

6.3.3. GBS Serotype-Specific IgM GMCs Before and 1 Month After Booster Vaccination

- Analysis population: Evaluable immunogenicity and mITT (provided there is a 10% or more difference with evaluable) populations (Section 4).

- Analysis time point: Before and 1 month after booster vaccination.

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Secondary objective.

- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.

- GMC of the IgM at each available time point for each serotype will be presented by vaccine group. For each vaccine group, the number of participants with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented.

6.3.4. GBS Serotype-Specific IgG1 GMFRs From Before to 1 Month After Booster Vaccination

- Analysis population: Evaluable immunogenicity population (Section 4).

- Analysis time points: Day 1 and 1 month after booster vaccination.

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Secondary objective.

- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.

- The number of participants with valid assay data (n), GMFRs of IgG1, and associated 2-sided 95% CIs will be presented for each serotype by vaccine group.

6.3.5. GBS Serotype-Specific IgM GMFRs From Before to 1 Month After Booster Vaccination

- Analysis population: Evaluable immunogenicity population (Section 4).

- Analysis time points: Day 1 and 1 month after booster vaccination.

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Secondary objective.

- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.

- The number of participants with valid assay data (n), GMFRs of IgM, and associated 2-sided 95% CIs will be presented for each serotype by vaccine group.

6.3.6. The Serotype-Specific GBS6 IgG Antibody Levels (GMC) and OPA (GMT) Data From the Primary C1091001 Study Might Be Combined With This Study to Assess the Immune Response Over Time

- Analysis population: Evaluable immunogenicity and mITT (provided there is a 10% or more difference with evaluable) populations. Participants from both the primary (C1091001) and booster (C1091007) evaluable immunogenicity populations will be included.

- Analysis time points: 1) Day 1 before vaccination and 1 week, 2 weeks, 1 month, 3 months, and 6 months after vaccination in the C1091001 study, 2) Before and 1 month after vaccination in the C1091007 study.

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Other objective.

- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.

- Figures of antibody line plots of IgG GMCs and OPA GMTs and the associated 95% CIs will be presented at each analysis time point by vaccine group, separately for each serotype. The participants from the C1091001 study will be combined with the C1091007 study participants based on whether they were assigned GBS6 with or without $AlPO_4$.

6.4. Subset Analyses

Subgroup analyses of the serotype-specific GBS6 IgG antibody levels by primary dose, baseline serotype-specific colonization status, sex, age group, or associated baseline IgG level may be performed provided that there are sufficient data to provide meaningful interpretation of the data. Subgroup analyses will be based on the evaluable immunogenicity population only.

- Analysis population: Evaluable immunogenicity population (Section 4).
- Analysis time point: Before and 1 month after booster vaccination.
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.
- Intercurrent event(s): For participants who discontinue or have major protocol violations, no observations following discontinuation or violation will be used. Results obtained from out-of-window blood draws will also be removed. Missing results will not be imputed.
- GMC of the IgG at each available time point for each serotype by baseline GBS prevaccination status by vaccine group. For each vaccine group, the number of participants with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented.

The subset definitions and relevant information on the analyses are summarized below in Table 7.

Table 7. Summary of Subset Analyses

Subgroup	Endpoint	Analysis Methodology	Analysis Time Points	Reporting Results
Serotype-specific colonization status at primary vaccination: positive or negative	Serotype-specific GMCs for IgG	Descriptive statistics	Day 1 (before vaccination) and 1 month after vaccination	Number, GMCs, and associated 95% CI by vaccine group
Sex: male or female	Serotype-specific GMCs for IgG	Descriptive statistics	Day 1 (before vaccination) and 1 month after vaccination	Number, GMCs, and associated 95% CI by vaccine group

Table 7. Summary of Subset Analyses

Subgroup	Endpoint	Analysis Methodology	Analysis Time Points	Reporting Results
Age group: 18-25 years, >25-40 years, and >40 years at primary vaccination	Serotype-specific GMCs for IgG	Descriptive statistics	Day 1 (before vaccination) and 1 month after vaccination	Number, GMCs, and associated 95% CI by vaccine group
Serotype-specific baseline IgG antibody level before primary vaccination: undetectable (< LLOQ) or detectable (≥ LLOQ)	Serotype-specific GMCs for IgG	Descriptive statistics	Day 1 (before vaccination) and 1 month after vaccination	Number, GMCs, and associated 95% CI by vaccine group
Serotype-specific baseline IgG antibody level before booster vaccination: undetectable (< LLOQ) or detectable (≥ LLOQ)	Serotype-specific GMCs for IgG	Descriptive statistics	Day 1 (before vaccination) and 1 month after vaccination	Number, GMCs, and associated 95% CI by vaccine group
Serotype-specific baseline IgG antibody level before primary vaccination: < C[a] vs ≥ C	Serotype-specific GMCs for IgG	Descriptive statistics	Day 1 (before vaccination) and 1 month after vaccination	Number, GMCs, and associated 95% CI by vaccine group
Serotype-specific baseline IgG antibody level before booster vaccination: < C[a] vs ≥ C	Serotype-specific GMCs for IgG	Descriptive statistics	Day 1 (before vaccination) and 1 month after vaccination	Number, GMCs, and associated 95% CI by vaccine group

Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.

a. The IgG levels of interest "C" will be 0.5 and 1.0 µg/mL.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

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

The number and proportion of participants with at least 1 medical history PT, arranged by SOC, will be tabulated for each vaccine group and the total sample. The medical history summary is based on the safety population.

Participant data listings for demography and baseline characteristics data will also be generated.

6.5.2. Study Conduct and Participant Disposition

The number and proportion of assigned participants will be included in the participant disposition summary. In addition, participants who completed each follow-up visit and 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, participants who missed at least 1 study procedure but continued in the study for safety follow-up will be summarized.

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

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

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

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

The protocol deviation listings will be generated. In addition, participants who do not receive the vaccine as assigned will be listed.

6.5.3. Study Treatment Exposure

Not applicable.

6.5.4. Concomitant Medications and Nondrug Treatments

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

Antipyretic medication taken prior to vaccination will be summarized separately.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of an investigational 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. As such, safety analysis is generally considered an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

AEs will be reported in accordance with the Pfizer reporting standards. For Tier 2 and Tier 3 events, the proportion of participants with AEs in each vaccine group will be presented. In addition, for Tier 2 AEs, 2-sided 95% CIs for the proportions of participants with AEs will be

constructed for each vaccine group. Tier 3 events will be summarized as part of the overall AE summary.

AEs, MAEs, and SAEs occurring after signing the informed consent and prior to booster vaccination will be summarized.

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

6.6.2. Laboratory Data

6.6.2.1. Clinical Safety Laboratory Assessments

Not applicable.

6.6.2.2. Pregnancy Testing

Data listings will be generated for the pregnancy outcomes.

6.6.3. Vital Signs

A descriptive summary based on the safety population will be provided in accordance with the Pfizer reporting standards and listings may be generated.

6.6.4. Physical Examination

A descriptive summary 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

As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

This study will be monitored by an E-DMC.

7.2. Interim Analyses and Summaries

No formal interim analysis will be conducted for this study.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. [redacted]

8. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.

2. Collett D. Modelling binary data. 1st ed. London: Chapman & Hall; 1991.

9. APPENDICES

9.1. Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
$AlPO_4$	aluminum phosphate
BLQ	below the limit of quantitation
CI	confidence interval
CRF	case report form
EC	ethics committee
e-diary	electronic diary
E-DMC	external data monitoring committee
FIH	first-in-human
GBS	group B streptococcus
GBS6	group B streptococcus 6-valent polysaccharide conjugate vaccine
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICD	informed consent document
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IgM	immunoglobulin M
IRB	institutional review board
LLOQ	lower limit of quantitation
MAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
OPA	opsonophagocytic activity
PT	preferred term
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
WHO	World Health Organization
WOCBP	woman/women of childbearing potential