Protocol C1091005

A PHASE 2B, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLINDED TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MULTIVALENT GROUP B STREPTOCOCCUS VACCINE WHEN ADMINISTERED CONCOMITANTLY WITH TETANUS, DIPHTHERIA, AND ACELLULAR PERTUSSIS VACCINE (TDAP) IN HEALTHY NONPREGNANT WOMEN 18 THROUGH 49 YEARS OF AGE

Statistical Analysis Plan (SAP)

Version: 1

Date: 14 Dec 2022

[redacted]

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 14 Dec 2022	Final protocol amendment 3, 04 Oct 2022	Not applicable	Not applicable

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C1091005. This SAP Version 1 is based on protocol amendment 3 dated 04-October-2022. 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. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary (Safety):	**Primary (Safety):**	**Primary (Safety):**
• To describe the safety and tolerability of GBS6 when administered concomitantly with Tdap (GBS6+Tdap) and when GBS6 is administered alone (GBS6+placebo).	In participants receiving at least 1 dose of the study interventions: • The proportion of participants reporting prompted local reactions within 7 days following study intervention administration. • The proportion of participants reporting prompted systemic events within 7 days following study intervention administration. • The proportion of participants reporting AEs through 1 month following study intervention administration.	• 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.

Objectives	Estimands	Endpoints
Primary (Safety):	**Primary (Safety):**	**Primary (Safety):**
	• The proportion of participants reporting MAEs and SAEs through 6 months following study intervention administration.	
Primary (Immunogenicity):	**Primary (Immunogenicity):**	**Primary (Immunogenicity):**
• To describe the immune responses induced by Tdap when administered concomitantly with GBS6 (GBS6+Tdap) compared to the immune responses induced by Tdap (placebo+Tdap) alone.	In participants receiving all doses of the study interventions and in compliance with the key protocol criteria (evaluable participants): • The difference in proportions of participants with anti–tetanus toxoid antibody concentrations ≥0.1 IU/mL measured 1 month after vaccination between the GBS6+Tdap group and the placebo+Tdap group. • The difference in proportions of participants with anti–diphtheria toxoid antibody concentrations ≥0.1 IU/mL measured 1 month after vaccination between the GBS6+Tdap group and the placebo+Tdap group. • GMR, estimated by the GMR of anti–pertussis toxin antibodies from the GBS6+Tdap group to the placebo+Tdap group measured 1 month after vaccination. • GMR, estimated by the GMR of anti-FHA antibodies from the GBS6+Tdap group to the placebo+Tdap group measured 1 month after vaccination. • GMR, estimated by the GMR of anti-PRN antibodies from the GBS6+Tdap group to the placebo+Tdap group measured 1 month after vaccination.	• Anti–tetanus toxoid and anti–diphtheria toxoid antibodies and anti–pertussis component (pertussis toxin, FHA, and PRN) antibodies.

Objectives	Estimands	Endpoints
Primary (Safety):	**Primary (Safety):**	**Primary (Safety):**
• To describe the immune responses induced by GBS6 when administered concomitantly with Tdap (GBS6+Tdap) compared to the immune responses induced by GBS6 (GBS6+placebo) alone.	• GBS CPS serotype-specific IgG GMR, estimated by the GMR of GBS CPS serotype-specific IgG antibodies from the GBS6+Tdap group to the GBS6+placebo group measured 1 month after vaccination.	• GBS CPS serotype-specific IgG antibody concentration.
Secondary:	**Secondary:**	**Secondary:**
• N/A	• N/A	• N/A
Exploratory (Immunogenicity):	**Exploratory (Immunogenicity):**	**Exploratory (Immunogenicity):**
• To further describe the immune responses elicited by Tdap when administered concomitantly with GBS6 (GBS6+Tdap) compared to Tdap (placebo+Tdap) alone.	In participants receiving all doses of the study interventions and in compliance with the key protocol criteria (evaluable participants): • Proportions of participants with anti–tetanus toxoid and anti–diphtheria toxoid antibody concentrations ≥0.1 IU/mL measured before vaccination and 1 month after vaccination for both the GBS6+Tdap group and the placebo+Tdap group. • Proportions of participants with anti–tetanus toxoid and anti–diphtheria toxoid antibody concentrations ≥1.0 IU/mL measured before vaccination and 1 month after vaccination for both the GBS6+Tdap group and the placebo+Tdap group. • The differences in proportions of participants with anti–tetanus toxoid and anti–diphtheria toxoid antibody concentrations ≥1.0 IU/mL measured 1 month after vaccination between the GBS6+Tdap group and the placebo+Tdap group.	• Anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibody concentrations.

Objectives	Estimands	Endpoints
Primary (Safety):	**Primary (Safety):**	**Primary (Safety):**
	• GMCs of anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibodies measured before vaccination and 1 month after vaccination for both the GBS6+Tdap group and the placebo+Tdap group. • GMFRs of anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibodies measured from before vaccination to 1 month after vaccination for both the GBS6+Tdap group and the placebo+Tdap group.	
• To further describe the immune responses elicited by GBS6 when administered concomitantly with Tdap (GBS6+Tdap) compared to GBS6 (GBS6+placebo) alone.	• GBS CPS serotype-specific IgG GMCs measured before and 1 month after vaccination for both the GBS6+Tdap group and the GBS6+placebo group. • GBS CPS serotype-specific IgG GMFRs measured from before vaccination to 1 month after vaccination for both the GBS6+Tdap group and the GBS6+placebo group.	• GBS CPS serotype-specific IgG antibody concentrations.

2.2.1. Primary Safety Estimands

The primary safety estimands for the primary objective will follow the treatment policy strategy from the EMA ICH E9 (R1) addendum[1] and estimate the safety percentages regardless of the occurrence of intercurrent event(s) or rescue medication use. The analyses will be based on the actual vaccine received.

Reactogenicity estimands after vaccination include the following attributes:

- Treatment: One of the dose/formulation levels defined as GBS6 (20 µg) and Tdap (GBS6+Tdap), GBS6 (20 µg) and placebo (GBS6+placebo), and Tdap and placebo (placebo+Tdap) (hereafter referred to as vaccine groups).
- Population: Healthy nonpregnant women 18 through 49 years old, inclusive, as defined by the study inclusion and exclusion criteria.
- Variable: Presence/absence and grade of any prespecified local reactions and systemic events within 7 days after vaccination.
- Intercurrent event(s): All collected data after the intercurrent event will be included; missing data will not be imputed.
- Population-level summary: Proportion of participants reporting prespecified local reactions and systemic events in each vaccine group.

AE, MAE, and SAE estimands after vaccination include the following attributes:

- Treatment: One of the dose/formulation levels defined as GBS6 (20 µg) and Tdap (GBS6+Tdap), GBS6 (20 µg) and placebo (GBS6+placebo), and Tdap and placebo (placebo+Tdap).
- Population: Healthy nonpregnant women 18 through 49 years old, inclusive, as defined by the study inclusion and exclusion criteria.
- Variables: Presence of AEs from the day of vaccination through 1 month after vaccination and presence of MAEs and SAEs from the day of vaccination through 6 months after vaccination.
- Intercurrent event(s): All collected data after the intercurrent event will be included; missing AE dates and missing AE severity will be handled according to Pfizer safety rules.
- Population-level summary: Proportion of participants reporting AEs, MAEs, and SAEs in each vaccine group.

2.2.2. Primary Immunogenicity Estimands

The primary immunogenicity estimands will use the hypothetical strategy to estimate the immune response when the intercurrent event would not occur. In other words, the immune response is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed.

Estimands for endpoints of anti–tetanus toxoid and anti–diphtheria toxoid antibodies include the following attributes:

- Treatment: One of the dose/formulation levels defined as GBS6 (20 µg) and Tdap (GBS6+Tdap) and Tdap and placebo (placebo+Tdap).
- Population: Healthy nonpregnant women 18 through 49 years old, inclusive, as defined by the study inclusion and exclusion criteria.
- Variable: Presence of anti–tetanus toxoid and anti–diphtheria toxoid antibody concentrations ≥0.1 IU/mL at 1 month after vaccination.
- Intercurrent event(s): The following intercurrent events could impact the interpretation or the measurement of the immune response:
    - The participant did not receive the study intervention as randomized.
    - The participant did not meet the study inclusion/exclusion criteria.
    - Major protocol violation – a protocol violation that, in the opinion of the sponsor's study medical monitor, would materially affect assessment of immunogenicity.
    - Blood was taken outside the window (<27 days or >45 days after vaccination).

    The clinical question of interest is based on whether the immune response elicited from Tdap via coadministration with GBS6, without any influence from any other immune-modifying drugs or vaccines, measured in a homogeneous time point, is noninferior to that of Tdap administered alone (ie, without GBS6). Therefore, all data after intercurrent events, if applicable and collected, will be excluded. Major protocol violations will be determined by clinical review.
    - Population-level summary: The differences and 2-sided 95% CI in proportions of participants with anti–tetanus toxoid and anti–diphtheria antibody concentrations ≥0.1 IU/mL at 1 month after vaccination between the GBS6+Tdap group and the placebo+Tdap group.

Estimands for endpoints of anti–pertussis component (pertussis toxin, FHA, and PRN) antibodies include the following attributes:

- Treatment: One of the dose/formulation levels defined as GBS6 (20 µg) and Tdap (GBS6+Tdap) and Tdap and placebo (placebo+Tdap).
- Population: Healthy nonpregnant women 18 through 49 years old, inclusive, as defined by the study inclusion and exclusion criteria.
- Variable: Anti–pertussis toxoid, anti-FHA, and anti-PRN antibody concentrations at 1 month after vaccination.
- Intercurrent event(s): The following intercurrent events could impact the interpretation or the measurement of the immune response:
    - The participant did not receive the study intervention as randomized.
    - The participant did not meet the study inclusion/exclusion criteria.
    - Major protocol violation – a protocol violation that, in the opinion of the sponsor's study medical monitor, would materially affect assessment of immunogenicity.
    - Blood was taken outside the window (<27 days or >45 days after vaccination).

    The clinical question of interest is based on whether the immune response elicited from Tdap via coadministration with GBS6, without any influence from any other immune-modifying drugs or vaccines, measured in a homogeneous time point, is noninferior to that of Tdap administered alone (ie, without GBS6). Therefore, all data after intercurrent events, if applicable and collected, will be excluded. Major protocol violations will be determined by clinical review.
- Population-level summary: The GMRs and 2-sided 95% CI estimated by the GMR of antipertussis, anti-FHA, and anti-PRN antibodies measured at 1 month after vaccination from the GBS6+Tdap group to the placebo+Tdap group.

Estimands for endpoints of GBS CPS serotype-specific IgG antibody concentration include the following attributes:

- Treatment: One of the dose/formulation levels defined as GBS6 (20 µg) and Tdap (GBS6+Tdap) and GBS6 (20 µg) and placebo (GBS6+placebo).
- Population: Healthy nonpregnant women 18 through 49 years old, inclusive, as defined by the study inclusion and exclusion criteria.

- Variable: GBS CPS serotype-specific IgG concentrations at 1 month after vaccination.

- Intercurrent event(s): The following intercurrent events could impact the interpretation or the measurement of the immune response:

  - The participant did not receive the study intervention as randomized.

  - The participant did not meet the study inclusion/exclusion criteria.

  - Major protocol violation – a protocol violation that, in the opinion of the sponsor's study medical monitor, would materially affect assessment of immunogenicity.

  - Blood was taken outside the window (<27 days or >45 days after vaccination).

  The clinical question of interest is based on whether the immune response elicited from GBS6 via coadministration with Tdap, without any influence from any other immune-modifying drugs or vaccines, measured in a homogeneous time point, is noninferior to that of GBS6 administered alone (ie, without Tdap). Therefore, all data after intercurrent events, if applicable and collected, will be excluded. Major protocol violations will be determined by clinical review.

- Population-level summary: The GMRs and 2-sided 95% CI estimated by the GMR of IgG concentration measured 1 month after vaccination from the GBS6+Tdap group to the GBS6+placebo group.

2.2.3. Secondary Estimands

Not applicable.

2.2.4. Exploratory Estimands

The exploratory immunogenicity estimands will use the hypothetical strategy and estimate immune responses induced by GBS6+Tdap, GBS6+placebo, and Tdap+placebo when the intercurrent event would not occur.

2.3. Study Design

2.3.1. Overall Design

This Phase 2, multicenter, placebo-controlled, randomized, observer-blinded study will enroll from US investigative sites approximately 300 healthy nonpregnant women, 18 through 49 years of age, who will be randomized to evaluate concomitant administration of GBS6 and Tdap. Participants will be randomized in a 1:1:1 ratio to receive 20 µg GBS6 and concomitant Tdap, 20 µg GBS6 and placebo, or Tdap and placebo.

Participants will have blood drawn prior to vaccination (Visit 1) and at 1 month after vaccination (Visit 2). E-diaries will be used to collect prompted local reaction and systemic event data for 7 days after vaccination (Days 1 through 7, where Day 1 is the day of vaccination). AEs will be collected through Visit 2. MAEs and SAEs will be collected through Visit 3.

Approximately 300 participants will be randomly assigned to the study interventions to achieve a target of 270 evaluable participants, assuming 10% no evaluability.

Participants will take part in the study from enrollment through approximately 6 months after vaccination.

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

An EDMC will be utilized.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

- Local reactions (pain at the injection site, redness, and swelling) within 7 days after administration of study interventions in each vaccine group.
- Systemic events (fever, fatigue, headache, nausea/vomiting, diarrhea, muscle pain, and joint pain) within 7 days after administration of study interventions in each vaccine group.
- AEs within 1 month after vaccination.
- MAEs and SAEs within 6 months after vaccination.

3.1.1.1. Local Reactions

During the reactogenicity e-diary reporting period following vaccination (Day 1 through Day 7, 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 reactogenicity e-diary. Local reactions will be assessed at the injection site on the left arm only.

If a local reaction persists beyond the end of the reactogenicity e-diary period following each vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21, and >21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, 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]	Potentially Life-Threatening (Grade 4)[b]
Pain at the 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
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)	>10.0 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
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)	>10.0 cm (≥21 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 e-diary but will be recorded as an AE on the CRF.
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.

Presence or Absence

The presence or absence of each local reaction (pain at the injection site, redness, and swelling) on a given day is defined as follows:

= Missing, if the value is missing on a given day;

= "Yes," if the participant reports the reaction as "yes" for redness or swelling or "mild," "moderate," "severe," or "Grade 4"(as per physical examination by a physician) for pain at the injection site on a given day;

= "No," if the participant reports the reaction as "no" for redness or swelling or "none" for pain at the injection site on a given day.

For each local reaction and any local reaction on any day, Table 3 details the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7.

Table 3. Derived Variables for Presence of Each and Any Local Reaction Within 7 Days

Variable[a]	Yes (1)	No (0)	Missing (.)
Presence of each local reaction.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7).	Participant reports the reaction as "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data on all 7 days (Day 1 through Day 7).
Presence of any local reaction.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" on all 7 days (Day 1 through Day 7) or as a combination of "no" and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data for all 3 local reactions on all 7 days (Day 1 through Day 7).

a. The variables will be derived for each and any of the local reactions (redness, swelling, and pain at the injection site) within the interval from Day 1 through Day 7 after vaccination.

Severity and Maximum Severity

For each local reaction reported, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7) as follows:

Maximum severity grade

= Missing, if values are missing for all days (Days 1-7);

= 0, if the participant reports all reactions as "no" or a combination of missing and "no" for all days (Days 1-7);

= *Highest grade* (maximum severity) within 7 days after vaccination, if the answer is not "no" for at least 1 day.

Duration (First to Last Day Reported)

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 Day

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, if participants report a change in severity of the local reaction, only the first day of reporting that specific local reaction will be counted.

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

1. Presence or absence of each local reaction on each day (Day 1-7) after vaccination.
2. Presence or absence of each local reaction on "any day (Day 1-7)" after vaccination.
3. Maximum severity of each local reaction on "any day (Day 1-7)" after vaccination.
4. Presence or absence of any local reaction on "any day (Day 1-7)" 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.

3.1.1.2. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, 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 7 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.

Table 4. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially Life-Threatening (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	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]	Potentially Life-Threatening (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

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 e-diary but will be collected as an AE on the CRF.
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.

The derivations for systemic events will be handled similarly to the way local reactions are handled for presence of the event, severity level, duration, and onset day. The variables associated with the systemic events will be computed similarly to the way local reactions are computed (see Section 3.1.1.1).

3.1.1.3. Fever

Oral temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection period when fever is suspected. 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 reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Fever will be grouped into ranges for the analysis according to Table 5.

In the event of a fever on Day 7, 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 ≥102.1°F (≥39.0°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 ≥102.1°F is entered into an e-diary.

Table 5. Scale for Fever

100.4°F to 101.1°F (≥38.0°C to 38.4°C)
101.2°F to 102.0°F (>38.4°C to 38.9°C)
102.1°F to 104.0°F (>38.9°C to 40.0°C)
>104.0°F (>40.0°C)

Note: Fever is defined as an oral temperature ≥100.4°F (≥38.0°C).

3.1.1.4. Use of Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study interventions will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 through Day 7).

For the use of antipyretic medication from Day 1 through Day 7, the following endpoints and variables will be derived for analysis following the same rules as for local reactions (see Section 3.1.1.1), where applicable:

- Presence (yes or no) of use of antipyretic medication on each day (Day 1-7).
- Presence (yes or no) of use of antipyretic medication on any day (Day 1-7).
- Duration (first to last day reported) of use of antipyretic medication.
- Onset day of use of antipyretic medication.

The use of antipyretic medication will be summarized and included in the systemic event summary tables but will not be considered a systemic event.

3.1.1.5. Adverse Events

All AEs, including nonserious AEs and SAEs, will be collected on the CRF and will be categorized according to the current version (at the time of reporting) of 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 study intervention), through and including Visit 2 (1 month after vaccination) for AEs, and through and including Visit 3 (6 months after vaccination) for MAEs and SAEs.

Immediate AEs, defined as AEs occurring within the first 30 minutes after study intervention administration, will be assessed and documented on the source documents, on the AE page of the CRF, and on an SAE form as applicable. The time of onset will be recorded for any AEs that occur on the same day as study intervention 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).

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 PT is defined as a Tier 2 event if there are 4 or more participants in at least 1 vaccine group reporting the event. Descriptive summary statistics (counts and proportions) will be provided for Tier 3 events for each vaccine group.

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

3.1.2. Primary Immunogenicity Endpoints

- Anti–tetanus toxoid and anti–diphtheria toxoid antibodies and anti–pertussis component (pertussis toxin, FHA, and PRN) antibodies.
- GBS CPS serotype-specific IgG antibody concentrations.

3.2. Secondary Endpoints

Not applicable.

3.3. Exploratory Endpoints

3.3.1. Exploratory Immunogenicity Endpoints

- Anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibody concentrations.
- GBS CPS serotype-specific IgG antibody concentrations.

3.4. Baseline Variables

Day 1 is defined as the day of vaccination and the start of the reporting period for all endpoints.

Day 1 is considered the baseline visit for the immunogenicity assessments.

Day 1 is the start of the reporting period for local reactions/systemic events. For prespecified systemic events, a baseline assessment related to the 1-week period prior to vaccination will also be recorded in the e-diary.

3.4.1. Demographic Characteristics

The participant demographic characteristics, including date of birth, sex, race, and ethnicity, will be collected. The full date of birth will be collected to critically evaluate the immune response and safety profile by age. In cases where more than 1 category is selected for race, the participant will be counted under the category "multiracial" for analysis.

Age (in years) will be derived based on the participant's birthday and the day of vaccination. For example, if the vaccination day is 1 day before the participant's 66th birthday, the participant is considered to be 65 years old. For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of vaccination for the age calculation. If the randomization date is also missing, then the informed consent date will be used for the age calculation.

3.4.2. Medical History

Medical history of clinical significance will be collected. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF. Medical history will be categorized according to MedDRA.

3.4.3. Physical Examinations

Physical examination will be performed to evaluate any clinically significant abnormalities at Visit 1. Abnormal results must be recorded on source documents and the Physical Examination page of the CRF.

3.4.4. E-Diary Completion

For all participants, an e-diary will be considered transmitted if any data for local reactions, systemic events, or use of antipyretic medication are present for any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

3.4.5. Vital Signs

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

3.4.6. Prior/Concomitant Vaccines and Concomitant Medications

The name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD through Visit 3 will be collected and recorded in the CRF. Antibiotic treatment taken from the signing of the ICD through Visit 3 will also be recorded.

Details of any medications that the participant is currently taking for medical conditions at enrollment (time of signing of the ICD at Visit 1) will be recorded in the CRF. Additionally, only medications taken to treat AEs from the signing of the ICD through Visit 2, and MAEs and SAEs from the signing of the ICD through Visit 3, will be recorded in the CRF.

3.5. Safety Endpoints

Local reaction, systemic event, AE, MAE, and SAE assessments are described above in the Primary Safety Endpoints section (Section 3.1.1).

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 unblinding and releasing the database, and classifications will be documented per standard operating procedures. For purposes of analysis, the populations are defined below:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to study intervention	All participants who are assigned a randomization number in the IWR system.
Evaluable	All participants who: • Are eligible (have signed the ICD and met all inclusion/exclusion criteria); • Receive all doses of the study interventions to which they were randomized at Day 1; • Have blood drawn for assay testing at Visit 2 (1 month after vaccination) within 27 to 45 days, inclusive; • Have at least 1 valid and determinate assay result at the 1-month postvaccination visit; and • Have no major protocol violations. The evaluable population will be the primary population for all immunogenicity data analyses.
mITT	All randomized participants who: • Receive at least 1 dose of the study interventions and • Have at least 1 valid and determinate assay result after vaccination.
Safety	All participants who: • Receive at least 1 dose of the study interventions and • Have at least 1 valid postdose safety assessment.

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 sponsor's study medical monitor, 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 study medical monitor will identify those participants with protocol violations before any immunogenicity analysis is carried out.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses in the study.

5.2. General Methods

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Completely missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

For all the immunogenicity endpoints, the analysis will be based on the evaluable population.

An additional analysis may be performed based on the mITT population if there is a large enough difference in sample size between the mITT population and the evaluable population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

5.2.1. Analyses for Binary Endpoints

Descriptive statistics for the binary variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for the binary endpoints of each group will be computed using the F distribution (Clopper and Pearson method).[2]

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).[3]

The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[4]

5.2.2. Analyses for Continuous Endpoints

Unless otherwise stated, descriptive statistics for the continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.2.1. Geometric Means

The GMCs of antibody concentrations will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to the Student t distribution, and then exponentiating the confidence limits.

5.2.2.2. Geometric Mean Fold Rises

GMFR will be calculated as the mean difference of an individual participant's logarithmically transformed antibody levels (postvaccination minus baseline) and transformed back to the original units. 95% CI will be computed by back transformation of the 95% CI using the Student t distribution for the mean difference of measures on the logarithmically transformed assay results.

5.2.2.3. Geometric Mean Ratios

GMR of the GBS6+Tdap group to the placebo+Tdap group for the anti–pertussis toxin, anti-FHA, and anti-PRN antibody concentrations at 1 month after vaccination will be calculated, along with associated 2-sided 95% CIs. The GMR will be calculated as the group mean difference of logarithmically transformed antibody levels and transformed back to the original units. Two-sided 95% CIs will also be obtained by calculating CIs using the Student t distribution for the mean difference of measures on the logarithmically transformed assay results and transforming confidence limits back to the original units.

5.2.2.4. Reverse Cumulative Distribution Curves

GBS CPS serotype specific empirical RCDCs for IgG antibody concentrations at 1 month after vaccination will be presented, for both the GBS6+Tdap and GBS6+placebo groups.

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with the line first going down and then to the right to the next assay value.

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 Pfizer's Vaccine Statistics Rulebook.

5.3.1.1. Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 7-day e-diary is available, the "any day (Days 1-7)" data will be considered nonmissing.

The reactogenicity data are collected through the 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 nonmissing. No missing reactogenicity data will be imputed other than what is described in Section 3.1.1.

5.3.2. Immunogenicity Data

CCI [redacted]

Values that are designated as serum QNS, IND, or "not done" will be set to missing. No imputation will be done for these missing values.

LLOQ results for each assay used in this study will be included in the analysis specification once they are available.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimand: The proportion of participants reporting local reactions (redness, swelling, and pain at the injection site) for up to 7 days following vaccination (Section 3.1.1.1).
- Estimand strategy: Treatment policy.
- Analysis set: Safety population (Section 4).
- Analysis time point: Day 1 through Day 7 after vaccination. Refer to Section 3.1.1.1 for maximum severity.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis. For participants who discontinue, all collected data will be included; intermediate missing values will not be imputed.
- Reporting results: The proportion, the numerator (n) and denominator (N) used for the calculation of the proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented, by vaccine group, for the following variables:
  - Presence or absence of each local reaction on each day (Day 1-7) after vaccination.
  - Presence or absence of each local reaction on “any day (Day 1-7)” after vaccination.
  - Presence or absence of any local reaction on “any day (Day 1-7)” after vaccination.
  - Maximum severity of each local reaction on “any day (Day 1-7)” after vaccination.

  The n, mean, standard deviation, 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.

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimand: The proportion of participants reporting systemic events (fever, fatigue, headache, nausea/vomiting, diarrhea, muscle pain, and joint pain) for up to 7 days following vaccination (Section 3.1.1.2).
- Estimand strategy: Treatment policy.
- Analysis set: Safety population (Section 4).
- Analysis time point: Day 1 through Day 7 after vaccination. Refer to Section 3.1.1.1 for maximum severity.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: The participants without any e-diary data throughout the 7 days after vaccination will be excluded from the analysis. For participants who discontinue, all collected data will be included; intermediate missing values will not be imputed.
- Reporting results: The proportion, the numerator (n) and denominator (N) used for the calculation of the proportion, and associated 2-sided Clopper-Pearson 95% CI will be presented, by vaccine group, for the following variables:
  - Presence or absence of each systemic event on each day (Day 1-7) after vaccination.
  - Presence or absence of each systemic event on "any day (Day 1-7)" after vaccination.
  - Presence or absence of any systemic event on "any day (Day 1-7)" after vaccination.
  - Maximum severity of each systemic event on "any day (Day 1-7)" after vaccination.

  The n, mean, standard deviation, 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.
- The use of antipyretic medication (see Section 3.1.1.4) will be summarized similarly to systemic events, except that there is no severity level associated with the use of antipyretic medication.

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The proportion of participants reporting AEs through 1 month after vaccination.
- Estimand strategy: Treatment policy.
- Analysis set: Safety population (Section 4).
- Analysis time point: Day 1 through 1 month after vaccination.
- Analysis methodology: Descriptive summary statistics for Tier 3 events; difference and 95% CI between the vaccine groups for Tier 2 events. No Tier 1 events are identified.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.
- Reporting results: 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 AEs, immediate AEs, severe AEs, related AEs, and AEs leading to withdrawal, for each SOC, and each PT within each SOC, by vaccine group. For AEs classified as Tier 2, the 95% CIs for the difference in the proportion of participants reporting events between the GBS6+Tdap group and the GBS6+placebo group, and between the GBS6+Tdap group and the placebo+Tdap group, will be calculated using the Miettinen and Nurminen method.[4] In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in the proportion of participants reporting events based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed.

6.1.1.4. Medically Attended Adverse Events and Serious Adverse Events

6.1.1.4.1. Main Analysis

- Estimand: The proportion of participants reporting MAEs and SAEs through 6 months after vaccination.
- Estimand strategy: Treatment policy.
- Analysis set: Safety population (Section 4).
- Analysis time point: Day 1 through 6 months after vaccination.
- Analysis methodology: Descriptive summary statistics for Tier 3 events; difference and 95% CI between the vaccine groups for Tier 2 events. No Tier 1 events are identified.

- Intercurrent events and missing data: For participants who discontinue, all collected data will be included; missing MAE and SAE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

- Reporting results: The number of participants with MAEs and SAEs within 6 months after vaccination (n), proportion, and associated 2-sided exact 95% CI will be presented for any SAE and any MAE for each SOC, and each PT within each SOC, by vaccine group.

6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. Anti–Tetanus Toxoid and Anti–Diphtheria Toxoid Antibody Concentrations Measured 1 Month After Vaccination

6.1.2.1.1. Main Analysis

- Estimand: Proportions of participants with anti–tetanus toxoid antibody concentrations ≥0.1 IU/mL at 1 month after vaccination and proportions of participants with anti–diphtheria toxoid antibody concentrations ≥0.1 IU/mL at 1 month after vaccination for the GBS6+Tdap and placebo+Tdap groups.

- Estimand strategy: Hypothetical strategies.

- Analysis set: Evaluable population (Section 4).

- Analysis time point: Month 1 after vaccination.

- Analysis methodology: Descriptive summary statistics.

- Intercurrent event(s): Missing serology results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

- Reporting results:

    - The differences (GBS6+Tdap group minus placebo+Tdap group) in proportions of participants with anti–tetanus toxoid antibody concentrations ≥0.1 IU/mL at 1 month after vaccination will be calculated, and the associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method.[4]

    - The differences (GBS6+Tdap group minus placebo+Tdap group) in proportions of participants with anti–diphtheria toxoid antibody concentrations ≥0.1 IU/mL at 1 month after vaccination will be calculated and associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method.[4]

6.1.2.2. Anti–Pertussis Toxin, Anti-FHA, and Anti-PRN Antibody Concentrations at 1 Month After Vaccination

6.1.2.2.1. Main Analysis

- Estimand: GMRs of antibodies from the GBS6+Tdap group to the placebo+Tdap group measured 1 month after vaccination.
- Estimand strategy: Hypothetical strategies.
- Analysis set: Evaluable population (Section 4).
- Analysis time point: Month 1 after vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing serology results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results: GMRs of the GBS6+Tdap group to the placebo+Tdap group for the anti–pertussis toxin, anti-FHA, and anti-PRN antibody concentrations at 1 month after vaccination will be descriptively summarized, along with associated 2-sided 95% CIs.

6.1.2.3. GBS Capsular Polysaccharide Serotype-Specific IgG 1 Month After Vaccination

6.1.2.3.1. Main Analysis

- Estimand: GMRs of GBS CPS serotype-specific IgG antibodies from the GBS6+Tdap group to the GBS6+placebo group measured 1 month after vaccination.
- Estimand strategy: Hypothetical strategies.
- Analysis set: Evaluable population (Section 4).
- Analysis time point: Month 1 after vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent event(s): Missing serology results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results: GMRs of GBS CPS serotype-specific IgG antibodies of the GBS6+Tdap group to the GBS6+placebo group at 1 month after vaccination will be descriptively summarized, along with associated 2-sided 95% CIs.

6.2. Secondary Endpoints

Not applicable.

6.3. Exploratory Endpoints

The analyses related to exploratory endpoints will be carried out if relevant data are available.

6.3.1. Exploratory Immunogenicity Endpoints

6.3.1.1. Anti–Tetanus Toxoid and Anti–Diphtheria Toxoid Antibody Concentrations

6.3.1.1.1. Main Analysis

- Estimand: Proportions of participants with anti–tetanus toxoid antibody concentrations and anti–diphtheria toxoid antibody concentrations ≥ certain thresholds before vaccination and at 1 month after vaccination for the GBS6+Tdap and placebo+Tdap groups.
- Estimand strategy: Hypothetical strategies.
- Analysis set: Evaluable population (Section 4).
- Analysis time points: Before vaccination and Month 1 after vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: Missing serology results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results:
    - Point estimates and the exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants with anti–tetanus toxoid and anti–diphtheria toxoid antibody concentrations ≥ certain thresholds before vaccination and at 1 month after vaccination for the GBS6+Tdap and placebo+Tdap groups. The thresholds include 0.1 and 1.0 IU/mL.
    - The differences (GBS6+Tdap group minus placebo+Tdap group) in proportions of participants with anti–tetanus toxoid and anti–diphtheria toxoid antibody concentrations ≥1.0 IU/mL at 1 month after vaccination will be calculated and associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method.[4]

6.3.1.2. Anti–Tetanus Toxoid, Anti-Diphtheria Toxoid, and Anti–Pertussis Component (Pertussis Toxin, FHA, PRN, and FIM) Antibody Concentrations

6.3.1.2.1. Main Analysis

- Estimand: GMCs of anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibodies measured before vaccination and 1 month after vaccination and GMFRs of anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibodies from before vaccination to 1 month after vaccination for both the GBS6+Tdap group and the placebo+Tdap group.
- Estimand strategy: Hypothetical strategies.
- Analysis set: Evaluable population (Section 4).
- Analysis time points: Before vaccination and Month 1 after vaccination.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: Missing serology results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results:
  - GMCs of anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibodies before vaccination and at 1 month after vaccination will be descriptively summarized for both the GBS6+Tdap group and the placebo+Tdap group, along with associated 2-sided 95% CIs.
  - GMFR from before vaccination to 1 month after vaccination will be provided for anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibodies for both the GBS6+Tdap and placebo+Tdap groups, along with associated 2-sided 95% CIs.

6.3.1.3. GBS CPS Serotype-Specific IgG Antibody Concentrations

6.3.1.3.1. Main Analysis

- Estimand: GBS CPS serotype-specific IgG GMCs measured before and 1 month after vaccination and GMFRs measured from before vaccination to 1 month after vaccination for both the GBS6+Tdap group and the GBS6+placebo group.
- Estimand strategy: Hypothetical strategies.
- Analysis set: Evaluable population (Section 4).

- Analysis time points: Day 1 and Month 1.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: Missing serology results will not be imputed, as MCAR is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.
- Reporting results:
    - GBS CPS serotype-specific IgG GMCs before vaccination and 1 month after vaccination will be descriptively summarized for the GBS6+Tdap and GBS6+placebo groups, along with associated 2-sided 95% CIs.
    - GBS CPS serotype-specific IgG GMFRs from before vaccination to 1 month after vaccination will be descriptively summarized for the GBS6+Tdap and GBS6+placebo groups, along with associated 2-sided 95% CIs.
    - GBS CPS serotype specific empirical RCDCs for IgG antibody concentrations at each available postvaccination time point will be presented, for both the GBS6+Tdap and GBS6+placebo groups.

6.4. Subset Analyses

Not applicable.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics and Medical History

Descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, and ethnicity) will be generated by vaccine group and for 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 for 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.

Each reported medical history term will be mapped to an SOC and PT according to MedDRA. The number and percentage of vaccinated participants having at least 1 diagnosis, overall and at each SOC and PT level, will be summarized by vaccine group based on the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. E-Diary Completion

For any given day, an e-diary will be transmitted and considered complete if all expected data (the 3 local reactions, the 7 systemic events, including fever, and the use of antipyretic medications) are available. If any of the items in the e-diary are missing on a specific day, the e-diary will not be transmitted, and the e-diary data will be missing for all items on that day. There is no possibility of partial filling of 1-day e-diary data. The e-diary completion (or transmission) rate will be provided after each vaccination on "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," and "Day 7." The denominator will be the total number of participants who received the vaccination, and the numerator will be the total number of participants with e-diary data transmitted on a given day. Additional e-diary compliance parameters will be derived as follows for the presence or absence of each local reaction on each day (Day 1-7) after vaccination:

1. E-diaries are completed for at least 1 day. The numerator is the number of participants who completed (transmitted) the e-diary on any day, and the denominator is the total number of participants who received a vaccination.

2. E-diaries are completed for at least 2 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 2 days, and the denominator is the total number of participants who received a vaccination.

3. E-diaries are completed for at least 3 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 3 days, and the denominator is the total number of participants who received a vaccination.

4. E-diaries are completed for at least 4 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 4 days, and the denominator is the total number of participants who received a vaccination.

5. E-diaries are completed for at least 5 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 5 days, and the denominator is the total number of participants who received a vaccination.

6. E-diaries are completed for at least 6 days. The numerator is the number of participants who completed (transmitted) the e-diary on any 6 days, and the denominator is the total number of participants who received a vaccination.

7. E-diaries are completed for all 7 days. The numerator is the number of participants who completed (transmitted) the e-diary on all 7 days, and the denominator is the total number of participants who received a vaccination.

The number and proportion of participants with e-diary data not transmitted, transmitted by day (Days 1-7), and transmitted on all days will be summarized by vaccine group and for the total sample.

6.5.2.2. Participant Disposition

The number and proportion of randomized 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 population and mITT population will also be summarized with reasons for exclusion.

The number and proportion of participants randomized, 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 for 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 population and mITT population will be generated separately.

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

6.5.3. Study Vaccination Exposure

Not applicable.

6.5.4. Concomitant Medications and Nonstudy Vaccinations

Nonstudy vaccines and medications taken after signing the ICD 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.

Antipyretic medication taken prior to vaccination will be summarized separately.

The name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD through Visit 3 will be collected and recorded in the CRF. Antibiotic treatment taken from the signing of the ICD through Visit 3 will be recorded.

Details of any medications that the participant is currently taking for medical conditions at enrollment (time of signing of the ICD at Visit 1) will be recorded in the CRF. Additionally, only medications taken to treat AEs from the signing of the ICD through Visit 2, and MAEs and SAEs from the signing of the ICD through Visit 3, will be recorded in the CRF.

6.6. Safety Summaries and Analyses

Local reaction, systemic event, AE, MAE, and SAE summaries are described under Primary Endpoints (Section 6.1).

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a study intervention 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.

Analyses and summaries of primary AE endpoints using the 3-tier approach are described in detail in Section 6.1.1.3 and Section 6.1.1.4.

6.6.1. 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.

6.6.2. 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

An interim analysis will be performed to assess efficacy and safety after Visit 2 has occurred for all enrolled participants. Interim analysis results may be used for internal business decisions regarding future study planning, stopping for futility, or stopping for early success.

This study will use an EDMC. Refer to Section 7.3 for further details.

7.2. Interim Analyses

There will be 1 planned interim analysis when Visit 2 (1-month postvaccination visit) safety and immunogenicity data from all participants are available. A final analysis will be performed after all participants complete the study and when all the data are available.

7.3. Data Monitoring Committee or Other Independent Oversight Committee

The analysis will be performed after all participants complete the study and when all the data are available.

This study will use an established EDMC. The EDMC is independent of the study team and includes only external members. The EDMC charter describes the role of the EDMC in more detail.

The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the EDMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

8. REFERENCES

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
BLQ	below the limit of quantitation
CI	confidence interval
CPS	capsular polysaccharide
CRF	case report form
e-diary	electronic diary
EDMC	external data monitoring committee
EMA	European Medicines Agency
FHA	filamentous hemagglutinin
FIM	fimbriae
GBS	group B streptococcus
GBS6	group B streptococcus 6-valent polysaccharide conjugate vaccine
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IND	indeterminate
IV	intravenous
IWR	interactive Web-based response
LLOQ	lower limit of quantitation
MAE	medically attended adverse event
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
PRN	pertactin
PT	preferred term
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SOC	system organ class
Tdap	tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine
US	United States
WHO	World Health Organization

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