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

Study Intervention Number:	PF-06760805
Study Intervention Name:	Group B Streptococcus 6-Valent Polysaccharide Conjugate Vaccine (GBS6)
US IND Number:	CCI
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Phase:	2b

Brief Title: Group B Streptococcus Vaccine and Concomitant Administration of Tdap in Nonpregnant Women

Document History

Document	Version Date
Amendment 3	04 October 2022
Amendment 2	11 April 2022
Amendment 1	22 January 2021
Original protocol	08 December 2020

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 3 (04 October 2022)

Overall Rationale for the Amendment: The addition of Visit 3 will be a 6-month safety follow-up telephone call. Visit 3 is added to address CBER's request for a 6-month safety follow-up.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis Section 1.3: Schedule of Activities Section 3: Objectives, Estimands, and Endpoints Section 4.1: Overall Design Section 5.2: Exclusion Criteria Section 6.5.3: Recording Nonstudy Vaccinations and Concomitant Medications Section 8.3.1: Time Period and Frequency for Collecting AE and SAE Information Section 8.3.5.1: Exposure During Pregnancy Section 8.11.3: Visit 3 – 6-Month Telephone Call Follow-up Visit (160-200 Days After Visit 1) Section 8.11.4: Unscheduled Visits	• The addition of Visit 3 will be a 6-month safety follow-up telephone call.	• A 6-month safety follow-up telephone call has been added to address CBER feedback.

Section # and Name	Description of Change	Brief Rationale
Section 9.1.2: Estimands Section 9.5: Interim Analyses Section 10.6: Appendix 6: Protocol Amendment History		

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale

Pfizer is developing a group B streptococcus 6-valent polysaccharide conjugate vaccine (GBS6) for the prevention of group B streptococcal invasive disease due to the 6 serotypes that cause the majority of disease in infants (serotypes Ia, Ib, II, III, IV, and V) by active immunization of pregnant women. Pregnant women have been vaccinated globally to prevent neonatal tetanus and pertussis in young infants, and to protect women and their infants against influenza.

Tetanus- and pertussis-containing vaccines are recommended in many countries during pregnancy. In the US, tetanus, diphtheria, and acellular pertussis vaccine (Tdap) is recommended for administration between 27 and 36 weeks of gestation. As GBS6 is being evaluated for administration within the same gestational timeframe, information on the safety and potential immune interference of concomitantly administered Tdap and GBS6 is important to understand prior to GBS6 licensure.

Study C1091005 is a descriptive study that will evaluate the concomitant administration of GBS6 and Tdap among nonpregnant women to rule out significant interference. The study is expected to provide useful data prior to the Phase 3 definitive coadministration assessment program in pregnant women.

Objectives, Estimands, and Endpoints

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 investigational products: • The proportion of participants reporting prompted local reactions within 7 days following investigational product administration. • The proportion of participants reporting prompted systemic events within 7 days following investigational product administration. • The proportion of participants reporting adverse events (AEs) through 1 month following investigational product administration. • The proportion of participants reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) through 6 months following investigational product 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 (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 investigational products 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. • Geometric mean ratio (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–filamentous hemagglutinin (anti-FHA) antibodies from the GBS6+Tdap group to the placebo+Tdap group measured 1 month after vaccination. • GMR, estimated by the GMR of antipertactin (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.
• 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 capsular polysaccharide (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 concentrations.

Objectives	Estimands	Endpoints
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 investigational products 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 at 1 month after vaccination between the GBS6+Tdap group and the placebo+Tdap group. • 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. • Geometric mean fold rise (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.	• Anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibody concentrations.

Objectives	Estimands	Endpoints
• 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.

Overall Design

This is a Phase 2, multicenter, placebo-controlled, randomized, observer-blinded study in which approximately 300 healthy nonpregnant women, 18 through 49 years of age, 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 (GBS6+Tdap), 20 µg GBS6 and placebo (GBS6+placebo), or Tdap and placebo (placebo+Tdap).

Participants will have blood drawn prior to vaccination (Visit 1) and at 1 month after vaccination (Visit 2). Electronic diaries (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.

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

Number of Participants

Approximately 300 participants will be randomly assigned to the investigational products to achieve a target of 270 evaluable participants, assuming 10% nonevaluability.

Intervention Groups and Duration

Participants will be enrolled and randomized in a 1:1:1 ratio to receive 1 of the following 3 groups: GBS6+Tdap, GBS6+placebo, or placebo+Tdap, to achieve a target of 270 evaluable participants, assuming 10% nonevaluability. Details of sample size determination can be found in Section 9.2.

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

Data Monitoring Committee

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

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC 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.

Statistical Methods

The statistical data analysis of the study results will be descriptive in nature. An estimation approach will be used to assess the safety and immunogenicity objectives in the study. Summary statistics will be provided for all binary and continuous endpoints related to study primary and exploratory objectives.

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. A summary of the planned statistical analyses of the primary and secondary endpoints can be found in Section 9.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Number	**1**	**2**	**3**
Visit Description	**Vaccination**	**1-Month Follow-up Visit**	**6-Month Follow-up Call**
Visit Window (Days)[a]	**Day 1**	**28-38 Days After Visit 1**	**160-200 Days After Visit 1**
Type of Visit	**Clinic**	**Clinic**	**Phone Call**
Obtain informed consent	X		
Assign a participant number using the IRT system	X		
Record demography, medical history, physical examination, vital signs[b]	X		
Perform urine pregnancy test	X		
Record nonstudy vaccine information	X	X	X
Record medication information	X	X[c]	X[c]
Review inclusion and exclusion criteria	X		
Measure prevaccination oral temperature	X		
Contraception check[d]	X	X	
Review temporary delay criteria	X		
Review continued eligibility		X	X
Assign randomization and container number	X		
Obtain blood draw for immunogenicity assessment[e]	X (~50 mL)	X (~50 mL)	
Administer investigational products	X		
Postvaccination observation (at least 30 minutes) and assessment of immediate AEs	X		
Issue/activate e-diary device[f]	X		
Issue thermometer and measuring device	X		

Visit Number	1	2	3
Visit Description	**Vaccination**	**1-Month Follow-up Visit**	**6-Month Follow-up Call**
Visit Window (Days)[a]	**Day 1**	**28-38 Days After Visit 1**	**160-200 Days After Visit 1**
Type of Visit	**Clinic**	**Clinic**	**Phone Call**
Provide the participant with a contact card	X		
Review and/or collect e-diary[g]		X	
Record AEs	X	X	
Record MAEs and SAEs	X	X	X

Abbreviations: AE = adverse event; IRT = interactive response technology; GBS = group B streptococcus; MAE = medically attended event; SAE = serious adverse event.

a. Day relative to start of study vaccination (Day 1).
b. Vital signs include weight, height, sitting blood pressure and pulse rate, respiratory rate, and temperature (oral).
c. Only concomitant medications taken to treat an AE, MAE, or SAE will be recorded in the case report form, as appropriate.
d. The contraception check is an opportunity to confirm that contraception is used consistently and correctly through the required time period per protocol (28 days after vaccination).
e. All blood volumes are approximate and at Visit 1 will be taken prior to vaccination.
f. Participants will record prompted reactogenicity events in an e-diary each evening for 7 days following vaccination (where Day 1 is the day of vaccination). Remind participants that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary. Ask participants to contact the investigator or site staff immediately if they are prompted by the e-diary from Day 1 through Day 7 following vaccination to determine if an unscheduled visit is required to assess a Grade 4 event.
g. Designated site staff will review e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review.

2. INTRODUCTION

GBS6 is being developed for:

- Active immunization to prevent disease caused by GBS serotypes (Ia, Ib, II, III, IV, and V) contained in the vaccine.

2.1. Study Rationale

GBS6 is being developed to address the global unmet medical need for prevention of infant GBS disease. It is based on the well-established platform of vaccines composed of CPSs conjugated to the CRM_{197} protein that target the polysaccharide capsules of encapsulated bacteria. Maternal immunization with an efficacious GBS vaccine would likely offer benefits beyond existing approaches to prevent infant GBS disease. The vaccine may also protect against adverse fetal outcomes by reducing GBS colonization in pregnant women. Pregnant women may also benefit directly from a GBS vaccine by the prevention of peripartum GBS disease. Other populations, such as adults of advanced age or with particular GBS risk factors, may be considered for GBS6 vaccine evaluation in the future.

Pregnant women are vaccinated globally to prevent neonatal tetanus and pertussis in young infants, and to protect women and their infants against influenza.

Tetanus- and pertussis-containing vaccines are recommended in many countries during pregnancy. In the US, tetanus, diphtheria, and acellular pertussis vaccine (Tdap) is recommended for administration between 27 and 36 weeks' gestation of each pregnancy. As GBS6 is being evaluated for administration within the same timeframe, information on the safety and potential immune interference of Tdap and GBS6 administered concomitantly are important to understand prior to evaluation of GBS6 in late-stage clinical trials and before GBS6 licensure.

Study C1091005 is a descriptive study that will evaluate the concomitant administration of GBS6 and Tdap among nonpregnant women to rule out significant interference. The study is expected to provide data prior to the Phase 3 definitive coadministration assessment program in pregnant women.

2.2. Background

2.2.1. Disease Overview

Streptococcus agalactiae, also known as GBS, is an encapsulated, gram-positive coccus that is associated with lower intestinal and rectovaginal colonization. There are 10 serotypes of GBS (Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX) differentiated by the composition of their polysaccharide capsule. Although all GBS serotypes have been found to cause disease, 6 serotypes (Ia, Ib, II, III, IV, and V) have been found to cause >95% of disease globally, with variability in their global prevalence and virulence.[1,2] GBS disease most frequently occurs in the very young—newborns and infants younger than 3 months of age—and the elderly, especially older adults with comorbid conditions.[3,4,5,6,7] However, GBS disease has been reported in individuals of all ages, and pregnant women may be particularly susceptible.[8]

Among infants, GBS may cause serious disease, including sepsis, meningitis, and pneumonia; less common manifestations include skin and soft tissue, bone, and joint infections.[9] In pregnant women, GBS may be associated with ascending infections ranging from relatively benign urinary tract infections to chorioamnionitis (which may result in stillbirth or preterm delivery) and puerperal sepsis (which may be fatal).[10] Bacteremia without a focus, cellulitis, bone and joint infections, and urinary tract infections are common disease manifestations of GBS infection in older nonpregnant adults.[6,11,12]

2.2.2. Maternal Immunization as an Approach to Prevent Disease in Infants and Pregnant Women

The goal of maternal immunization is to generate protective antibodies that may be placentally transferred in utero to provide the newborn and young infant with IgG antibody concentrations at birth sufficient to protect them against infections during the period of increased vulnerability until they are able to adequately respond to their own active immunizations or infectious challenges. Examples of this concept include vaccination with tetanus, pertussis, or influenza vaccines to provide maternally transferred antibody protection against the cognate pathogen. Pfizer is following this paradigm to develop vaccines for respiratory syncytial virus (RSV) and GBS infections.[13]

Vaccination of pregnant women is used globally in the prevention of neonatal tetanus and pertussis in young infants, and to protect women and their infants against influenza.[14,15,16,17,18] There is increasing experience with the safety, effectiveness, and acceptance of influenza vaccine and tetanus toxoid– and pertussis-containing vaccines for use in pregnant women in various regions globally to prevent disease in newborns and infants.[17,19,20] Maternal immunization against influenza is recommended by the US Advisory Committee on Immunization Practices (ACIP).[21] In addition, several countries recommend maternal Tdap vaccination during every pregnancy, including closely spaced pregnancies. To date, these vaccines have demonstrated an acceptable safety profile with single and repeat dosing.[22,23,24]

Current preventive measures against invasive GBS disease in infants vary by region and include universal screening of pregnant women in the third trimester of pregnancy and administration of intrapartum antibiotic prophylaxis (IAP) to prevent disease in the infant, a risk-based approach to IAP, or no prevention intervention.[7,9,25] Each of these approaches has limitations, and while implementation of IAP policies has reduced incidence of early-onset disease (EOD), there has not been a measurable impact on late-onset disease (LOD; beyond the first week of life) and a significant EOD burden remains. Published data from natural history studies have demonstrated a general correlation between maternal GBS antibody levels and a reduced risk of GBS disease in newborns, with an attempt made to derive an immunological threshold of protection.[26,27,28,29,30] These studies established clearly that antibodies to GBS capsular polysaccharides in the mother correlated with protection against GBS disease in the infant. Immunization of pregnant women with a GBS vaccine, therefore, is a reasonable alternative approach to prevent invasive GBS disease in young infants and possibly GBS disease in pregnant or postpartum women.[31] A licensed GBS vaccine approved for administration in pregnancy would likely be given in the second trimester and/or during the third trimester.

There is currently no licensed vaccine for the prevention of GBS disease; however, Pfizer is developing a multivalent vaccine for the prevention of invasive GBS disease in infants. GBS6 was evaluated in a Phase 1/2 first-in-human (FIH) study in healthy nonpregnant women and men 18 through 49 years of age in the US. GBS6 was safe and well-tolerated and elicited robust immune responses that persisted through 6 months after vaccination at all dose levels and formulations. No meaningful difference in the GBS CPS IgG immune responses were observed for any serotype between GBS6 doses or formulations. No safety risks were identified beyond reactogenicity through 6 months. The safety findings from this FIH study are similar to those of other investigational GBS vaccines and of other licensed vaccines recommended for use in pregnancy.[32,33,34,35]

The purpose of this Phase 2b descriptive study is to evaluate the concomitant administration of GBS6 and Tdap. The study is expected to provide data prior to the Phase 3 definitive coadministration assessment program in pregnant women, which will inform future studies with pregnant women in which Tdap may be used.

2.3. Benefit/Risk Assessment

Pfizer is developing GBS6 to address a global unmet medical need for the prevention of GBS disease due to 6 serotypes in young infants by active immunization of pregnant women. GBS6 is composed of polysaccharides of the 6 most prevalent serotypes causing >95% of GBS disease in infants and adults,[1,4] individually conjugated to the CRM_{197} carrier protein. An efficacious vaccine would offer a favorable adjunct option to currently existing approaches for GBS disease prevention by providing greater feasibility of implementation in low- and middle-income countries (LMICs), and the potential to provide protection against disease, including both EOD and LOD, in infants. In addition, there is a long history of success in protecting pediatric and adult populations against diseases caused by encapsulated bacteria using vaccines that target CPSs and generate functional antibodies that eliminate bacteria by opsonophagocytosis.

A completed Phase 1/2 study of GBS6 in healthy adults demonstrated that GBS6 was safe and well-tolerated in healthy nonpregnant women and healthy men and elicited robust immune responses that persisted through 6 months after vaccination at all dose levels and formulations evaluated. The study's safety findings were similar to those of other investigational GBS and licensed vaccines recommended for use in pregnancy. The data provide support for continuing evaluation of GBS6 in later-phase trials and in pregnant women.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GBS6 may be found in the GBS6 investigator's brochure (IB), which is the SRSD for this study.

The SRSD for Tdap will be the product information for the US, where this vaccine will be procured.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) – GBS6, Tdap, and Placebo		
Potential risks associated with GBS6 in the age group for this study include the following: • Injection site redness • Injection site swelling • Injection site pain or tenderness • Fever As with any vaccine, a rare but possible event associated with GBS6 is: • Hypersensitivity reaction, including swelling of the face or lips (face edema), wheezing (bronchospasm), or difficulty in breathing (dyspnea)	The potential risks are based on the FIH C1091001 study results and those described in the IB.	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). Individuals with significant reactions after vaccination or AEs considered by the investigator to present increased risk to the participant or who develop exclusionary conditions during the conduct of the study will be excluded from interventions but may be followed for safety.
Potential risks associated with Tdap in the age group for this study include the following: • Injection site pain • Injection site swelling • Injection site redness • Headache • Body ache or muscle weakness	The risks are based on the known safety profile of a commonly used Tdap in this age group, presented in the Adacel USPI.	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). Individuals with significant reactions after vaccination or AEs considered by the investigator to present increased risk to the participant or who develop exclusionary conditions during the conduct of the study will be excluded from interventions but may be followed for safety.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) – GBS6, Tdap, and Placebo		
Potential risks associated with placebo in the age group for this study include the following: • Injection site pain • Injection site swelling • Injection site redness	The risks are based on commonly observed events in vaccine studies using a placebo.	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). Individuals with significant reactions after vaccination or AEs considered by the investigator to present increased risk to the participant or who develop exclusionary conditions during the conduct of the study will be excluded from interventions but may be followed for safety.
Study Procedures – Venipuncture		
Venipuncture will be performed during the study.	There is a risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site and an overall risk of dizziness and fainting associated with the procedure.	Only qualified nurses, physicians, nurse practitioners, physician's assistants, phlebotomists, or medical assistants certified or otherwise authorized to draw blood per the standards and procedures of the investigative site as allowed by institutional, local, and state guidance will be allowed to draw blood to minimize local complications.

2.3.2. Benefit Assessment

GBS6 is being developed to benefit infants through the vaccination of pregnant women. The current study will provide important information about interference of GBS6 and Tdap in nonpregnant women to inform future studies in pregnant women. Nonpregnant women may benefit from participation in this study from the development of GBS antibodies, which may protect them from GBS disease in the near future.

Other benefits to the individual participant may include receipt of a booster Tdap and protection from Tdap-associated disease, physical examination by a medical provider at the start of the study and prior to each study vaccination, a thorough review of the participant's vaccination status, and evaluation and management of some illnesses (AEs) that occur during participation in the study as part of protocol-specified scheduled and unscheduled assessments.

2.3.3. Overall Benefit/Risk Conclusion

The anticipated benefit (protective immunity against GBS6) that may be afforded to participants outweighs the potential risks in this study, including the possibility of transient local and systemic reactogenicity events of varying severity and possible complications from needlesticks (vaccination or venipuncture) for an overall favorable benefit/risk assessment.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

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 investigational products: • The proportion of participants reporting prompted local reactions within 7 days following investigational product administration. • The proportion of participants reporting prompted systemic events within 7 days following investigational product administration. • The proportion of participants reporting adverse events (AEs) through 1 month following investigational product administration. • The proportion of participants reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) through 6 months following investigational product 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 (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 investigational products 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. • Geometric mean ratio (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–filamentous hemagglutinin (anti-FHA) antibodies from the GBS6+Tdap group to the placebo+Tdap group measured 1 month after vaccination. • GMR, estimated by the GMR of antipertactin (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.
• 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 capsular polysaccharide (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

Objectives	Estimands	Endpoints
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 investigational products 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. • 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. • Geometric mean fold rises (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.	• Anti–tetanus toxoid, anti–diphtheria toxoid, and anti–pertussis component (pertussis toxin, FHA, PRN, and FIM) antibody concentrations.

Objectives	Estimands	Endpoints
• 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.

4. STUDY DESIGN

4.1. Overall Design

This Phase 2, multicenter, placebo-controlled, randomized, observer-blinded study will enroll approximately 300 healthy nonpregnant women from US investigative sites, 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.

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

An E-DMC will be utilized.

4.2. Scientific Rationale for Study Design

Refer to Section 2.1.

Human reproductive safety data are limited for GBS6.

Based on the pharmacology of the compound and data from reproductive toxicity in animals, there is no expectation of human teratogenicity. However, as data in humans are limited, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

The dose of vaccine that will be used in this study was determined following assessment of safety and immunogenicity data from the FIH study (C1091001) and Study C1091002.

The FIH study was conducted in healthy nonpregnant women and healthy men in the US and assessed the safety and immunogenicity of 3 different dose levels of GBS6 (5, 10, or 20 µg/serotype, formulated with or without $AlPO_4$). GBS6 was safe and well-tolerated and elicited robust immune responses at all dose levels and formulations. The highest dose (20 µg/serotype, formulated without $AlPO_4$) is selected for this study, as this is the dose/formulation that has been selected for future licensure studies and has shown an acceptable safety profile, the greatest consistent postvaccination immune responses in pregnant women, and measurable IgG antibody concentrations in infants in Study C1091002.

4.4. 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.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Healthy women ≥18 and ≤49 years of age. Refer to Appendix 4 for reproductive criteria for female participants (Section 10.4.1).

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with scheduled visits, investigational plan, laboratory tests, lifestyle considerations, and other study procedures, including completion of the e-diary from Day 1 to Day 7 following administration of investigational product.

3. Healthy females at enrollment who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

4. Expected to be available for the duration of the study and who can be contacted by telephone during study participation.

Informed Consent:

5. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Pregnant female participants; breastfeeding female participants; positive urine pregnancy test for women of childbearing potential (WOCBP) at Visit 1 (prior to vaccination); and WOCBP who are, in the opinion of the investigator, sexually active and at risk for pregnancy; and WOCBP who are unwilling or unable to use effective methods of contraception as outlined in this protocol from the signing of the informed consent until at least 28 days after the last dose of investigational product.

Medical Conditions:

2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the investigational product or any diphtheria toxoid–containing or CRM_{197}-containing vaccine.

3. History of microbiologically proven invasive disease caused by group B streptococcus.

4. Immunocompromised participants with known or suspected immunodeficiency.

5. Bleeding diathesis or condition associated with prolonged bleeding that would in the opinion of the investigator contraindicate intramuscular injection.

6. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

7. Previous vaccination with any licensed or investigational GBS vaccine, or planned receipt during the participant's participation in the study (through the 6-month follow-up visit [Visit 3]).

8. Vaccination within 5 years with tetanus and diphtheria toxoids and acellular pertussis–containing vaccines (Tdap) before investigational product administration.

9. Participants who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt through the 1-month follow-up visit (Visit 2).

10. Vaccination with diphtheria- or CRM_{197}-containing vaccine(s) from 6 months before investigational product administration, or planned receipt through the 1-month follow-up visit.

11. Receipt or planned receipt of blood/plasma products or immunoglobulin, from 60 days before investigational product administration through the 1-month follow-up visit.

Prior/Concurrent Clinical Study Experience:

12. Participation in other studies involving investigational drug(s) within 28 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

13. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.3) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number if they later meet eligibility criteria.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

5.5.1. Temporary Delay Criteria

The following conditions are temporary or self-limiting and a participant may be vaccinated and/or have blood drawn in the study once the condition(s) has/have resolved and no other exclusion criteria are met. The prevaccination immunogenicity blood draw and vaccination should take place on the same day (Visit 1).

5.5.1.1. Criteria for Temporarily Delaying Vaccine Administration

- Current febrile illness (body temperature ≥100.4°F [≥38.0°C]) or other acute illness within 48 hours before investigational product administration.

- Receipt of any inactivated vaccine or otherwise nonlive vaccine within 14 days and any live vaccine within 28 days before investigational product administration.

- Receipt of short-term (<14 days) systemic corticosteroids. Investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 30 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

5.5.1.2. Criteria for Temporarily Delaying Blood Draw

- Receipt of antibiotic therapy within 72 hours before blood draw. Note: Topical antibiotics are permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

For this study, the investigational products are GBS6 (20 µg CPS/serotype/dose, which is equivalent to a 120-µg/0.5-mL dose), Tdap, and placebo (normal saline).

6.1.1. GBS6

GBS6 is composed of serotypes Ia, Ib, II, III, IV, and V CPSs individually conjugated to the CRM_{197} carrier protein. CCI [redacted]. There is 1 dose level (20 µg CPS/serotype/dose per vaccine dose of 120 µg).

CCI [redacted] designed to deliver the intended dose in a 0.5-mL injection volume.

6.1.2. Tdap

US-licensed Tdap will be provided by the sponsor to each study site.

Investigational sites will be provided with details of which US-licensed Tdap will be provided prior to the start of enrollment. The active ingredients of Tdap will contain the following (per 0.5-mL dose): 5 Lf (limits of flocculation) of TTd, 2 Lf of DTd, acellular pertussis antigens (2.5 µg of inactivated pertussis toxin, 5 µg of FHA, and 3 µg of PRN, 5 µg of FIM).

The Tdap will also contain the following excipient concentrations: 1.5 mg $AlPO_4$, ≤5 µg of residual formaldehyde, <50 ng residual glutaraldehyde, and 3.3 mg phenoxyethanol.

Note: The stopper of the Tdap vial may contain natural rubber latex.

6.1.3. Placebo

The placebo for the GBS6 vaccine and Tdap will be a sterile normal saline solution for injection (0.9% NaCl injection, in a 0.5-mL dose).

Placebo will be provided by the sponsor to each study site.

Placebo will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.

6.1.4. Administration

Participants will receive 2 injections at Visit 1 in accordance with the study's SoA.

A 120-µg dose of GBS6 (0.5 mL) and Tdap, a 120-µg dose of GBS6 (0.5 mL) and normal saline placebo, or normal saline placebo and Tdap will be administered intramuscularly by an unblinded site staff member or designee.

Location of Injection at Visit 1

Formulation	Site of Vaccination
GBS6 (20 µg CPS/serotype/dose) Tdap	Left deltoid muscle Right deltoid muscle
GBS6 (20 µg CPS/serotype/dose) Placebo	Left deltoid muscle Right deltoid muscle
Placebo Tdap	Left deltoid muscle Right deltoid muscle

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Investigational product will be shipped at +2°C to +8°C to each study site after required regulatory and legal documents have been received by the sponsor. Upon receipt at the study site, the investigational product should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage.

3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

6. Study interventions should be stored in their original containers.

7. See the IP manual for storage conditions of the study intervention.

8. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

9. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the investigational products for administration. Investigational products should be prepared and dispensed by an appropriately qualified and experienced unblinded member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to investigational product groups will proceed through the use of an IRT system (IWR). The unblinded site personnel will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The unblinded site personnel will then be provided with an investigational product assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored by the unblinded site personnel in the unblinded site files.

Study intervention will be dispensed at Visit 1 only as summarized in the SoA.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of the Site Personnel

This is an observer-blinded study, as the appearance of GBS6, Tdap, and placebo will not be matched. The study staff dispensing, preparing, and administering the vaccine will be unblinded, but all other study personnel, including the principal investigator and the participant, will be blinded. The principal investigator will assign the responsibility of unblinded dispenser and unblinded administrator to persons who will not participate in the evaluation of any study participant. More than 1 unblinded dispenser/administrator may be assigned. A member of the study site staff or clinic pharmacy should fulfill this role. Contact between the unblinded dispenser/administrator and study participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispenser/administrator must not be allowed to know the investigational product assigned to any study participant and must not be allowed to see the investigational product containers.

6.3.3. Blinding of the Sponsor

Sponsor study team members will remain blinded to vaccine assigned/received at the participant level. In an event that unblinded results need to be submitted for regulatory communications prior to study team unblinding, efforts will be made to ensure study team members involved in participant assessments are blinded.

Laboratory personnel performing the immunologic assays will remain blinded to vaccine assigned/received throughout the study.

6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's investigational product assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's investigational product assignment unless this could delay further management of the participant. If a participant's investigational product assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately qualified and designated study staff at the investigator site.

6.5. Concomitant Therapy

6.5.1. Prohibited Nonstudy Vaccines and Medications During the Study

- Nonstudy investigational vaccines, drugs, or medical devices are prohibited during the course of the study.

- Nonstudy diphtheria- and CRM_{197}-containing vaccines, blood/plasma products or immunoglobulins, and immunosuppressive therapy are prohibited during the course of the study.

- Other nonstudy vaccines may not be given concomitantly with the investigational product or within 14 days after investigational product administration (except during an outbreak or pandemic situation).

6.5.2. Permitted Nonstudy Vaccines and Medications During the Study

- Licensed influenza vaccine may be given during the study 14 days after investigational product administration.

- If medically necessary (eg, pandemic), licensed vaccines may be given at any time.

- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration is permitted during participant participation in the study.

- The use of prophylactic antipyretic medication, while permitted, is not recommended on the day of the investigational product administration.

- Any other vaccines that are medically required by local recommendations and permitted by the protocol may be administered concomitantly with GBS6 and/or Tdap but must be given in a different limb.

- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

6.5.3. Recording Nonstudy Vaccinations and Concomitant Medications

The name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD to Visit 3 will be collected and recorded in the CRF. Antibiotic treatment taken from the signing of the ICD to 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 (per Section 8.3.1).

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Withdrawn consent (refused further follow-up);

- Lost to follow-up;

- Medication error without associated AE;

- Death;

- Study terminated by sponsor;
- AEs;
- Protocol violation;
- Pregnancy;
- No longer meets eligibility criteria.

After investigational product administration at Visit 1, participants who request to discontinue further study procedures (eg, blood draw) at an upcoming visit will be asked to remain in the study for protocol-specified safety follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with her.

If a participant withdraws from the study, she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Vaccine SAE Reporting Form.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Participants who have received the investigational product will not be replaced regardless of the reason for withdrawal.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is only from further receipt of the study intervention or also from the study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit or cannot be reached for scheduled telephone call:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he/she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy and/or Immunogenicity Assessments

Blood samples (approximately 50 mL/visit) for immunogenicity assessments will be collected from all participants prior to vaccination (Day 1) and at 1 month after vaccination (Visit 2)

Sample collection, processing, storage, and shipping information can be found in the ISF or equivalent manual. Sera will be used for immunogenicity assessments, assay development, and routine assay maintenance.

8.1.1. GBS Vaccine Antibody Testing

Concentrations of anticapsular IgG for the 6 serotypes (Ia, Ib, II, III, IV, and V) will be determined from the GBS6+Tdap and GBS6+placebo groups for each blood sample at Day 1 and at 1 month after vaccination and reported as IgG concentrations.

Participants from these 2 groups will be identified by an independent unblinded statistician; additional participants from the placebo+Tdap group may be included in order to maintain the blinding of randomization assignment.

8.1.2. Tdap Antibody Testing

Sera will be collected from the coadministration and placebo+Tdap groups and they will be assayed for IgG antibodies to Tdap antigens in a multiplexed Luminex bead-based assay (DTP-6 IgG). IgG levels to diphtheria, tetanus, and pertussis antigens (pertussis toxin, PRN, FHA, and FIM) will be measured and reported in either IU/mL (diphtheria and tetanus) or EU/mL (pertussis toxin, FHA, FIM and PRN).

Participants from these 2 groups will be identified by an independent unblinded statistician; additional participants from the GBS6+placebo group may be included in order to maintain the blinding of randomization assignment.

Immunogenicity assays will be performed at Pfizer Vaccine Research & Development Laboratory located at 401 North Middletown Road, Pearl River, NY 10965 and/or at a facility designated by Pfizer.

8.1.3. Biological Samples

Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed.

The participant may request that her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Participant E-Diary

Participants will be required to use an e-diary, based on appropriate technology, and will be asked to monitor and record local reactions, systemic events, temperature, and antipyretic/pain medication used to treat symptoms each evening for 7 days following vaccination. Participants may be able to utilize their own devices to access this technology, or use a device provided by the sponsor. This system, hereafter referred to as the participant's e-diary, allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions, systemic events, temperature, and antipyretic/pain medication used to treat symptoms reported on the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting. These data do not need to be reported by the investigator in the CRF. However, if a participant withdraws because of prompted events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

Investigators (or appropriately qualified designee) are required to review the e-diary data online to evaluate participant compliance and as part of the ongoing safety review.

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 CRF.

8.2.2. Grading Scale for Prompted Events

The grading scales used in this study to assess AEs as described below are based on concepts outlined in the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[36]

8.2.2.1. Local Reactions

From Day 1 to Day 7, where Day 1 is the day of vaccination, participants will be asked to assess redness, swelling, and pain at the injection site of the left arm and to record the symptoms in the e-diary in the evening. Redness and swelling of the injection site of the left arm 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 1. 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 of the left arm will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 1. A participant with a severe (Grade 3 or above) local reaction of the left arm will be prompted to contact the investigator to perform an unscheduled visit and assess the reaction.

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. Site staff will educate the participant regarding signs and symptoms that would prompt site contact. The procedure for notification of the sponsor is provided in the study documentation.

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.

Table 1. 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)	>10.0 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)	>10.0 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 (Section 8.11.4) 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.

8.2.2.2. Systemic Events

From Day 1 to Day 7, 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 2. 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 2. 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
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 (Section 8.11.4) 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.

8.2.2.3. Fever

In order to record information on fever, a digital thermometer will be given to the participant with instructions on how to measure oral temperature at home. Temperature will be collected in the evening daily for 7 days following vaccination (Days 1 to 7, where Day 1 is the day of vaccination) and at any time during the 7 days that 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 e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature less than 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. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 3.

Table 3. Ranges for Fever

100.4°F to 101.1°F (38.0°C to 38.4°C)
101.2°F to 102.0°F (>38.4°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)

8.2.3. Use of Antipyretic/Pain Medication

From Day 1 to Day 7, where Day 1 is the day of vaccination, the participant will be asked to record the use of antipyretic and/or pain medication used to treat symptoms reported in the e-diary in the evening.

8.2.4. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

8.2.5. Pregnancy Testing

Pregnancy tests will be urine tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

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 the participant's 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.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection, which begins after obtaining informed consent, as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.

- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after vaccination.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion, including miscarriage and missed abortion;
- Neonatal deaths that occur within 6 months of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 6 months should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Reporting Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy in an approved indication should be reported as an SAE to Pfizer Safety.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Reporting Form **only when associated with an SAE.**

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;

- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than 1 dose within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Please refer to Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

If, because of a medical situation (such as disease outbreak or pandemic), study visits cannot be conducted in person at the study site, visit procedures should be conducted remotely or via telephone, as is feasible.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

8.11.1. Visit 1 – Vaccination (Day 1)

- Obtain written informed consent before performing any study-specific procedures.
- Assign a participant number using the IRT system.
- Obtain and record the participant demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record any medical history of clinical significance.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the Physical Examination page of the CRF.
- Prior to vaccination, perform a urine pregnancy test for WOCBP and ensure the result is negative.
- Record nonstudy vaccinations and medications as described in Section 6.5.3.
- Ensure and document that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- Prior to vaccination, measure vital signs, including weight, height, sitting blood pressure and pulse rate, respiratory rate, and temperature (oral).
- Verify the participant's understanding of and compliance with the protocol requirements for contraception. Instruct the participant to use appropriate contraceptives until 28 days after administration of investigational product and document the conversation and the participant's affirmation in the participant's source document.

- A blinded site staff member will use the IRT system to obtain the participant's randomization number. An unblinded site staff member will use the IRT to assign the investigational product container number, and will prepare the investigational product and deliver it to the investigational product administrator. Please refer to the IP manual for further instruction on this process.

- Prior to vaccination, collect a blood sample of approximately 50 mL for immunogenicity assessments.

- The unblinded administrator administers a 0.5-mL injection of investigational product into the deltoid muscle of the left arm and a 0.5-mL injection of investigational product into the deltoid muscle of the right arm (see Section 6.1.4). Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for at least 30 minutes after investigational product administration for any acute reactions. Record any immediate AEs in the participant's source documents, on the AE page of the CRF, and on an SAE form as applicable.

- Issue/activate e-diary device. Ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Issue the participant a measuring device to measure local reactions and a digital thermometer to measure daily temperatures, and provide instructions on their use.

- Ask the participant to contact the site staff or investigator immediately if she is prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring >20 measuring device units [>10.0 cm]). Remind participants that study staff may contact them to obtain additional information on Grade 3 (or above) events entered into the e-diary.

- Ask the participant to contact the site staff or investigator if an MAE (eg, emergency room) or hospitalization occurs.

- Provide the participant with a contact card (see Section 10.1.10 for a description of the contact card).

- Record AEs as described in Section 8.3.

- Complete the participant's source documents.

- The investigator or an authorized designee completes the CRF and an unblinded site staff member updates the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.2. Visit 2 – 1-Month Follow-up Visit (28-38 Days After Visit 1)

- Ensure that the participant continues to be eligible for the study, meets none of the participant withdrawal criteria as described in Section 7, and meets none of the blood draw temporary delay criteria as described in Section 5.5.1.2.
- Verify the participant's understanding of and compliance with the protocol requirements for contraception.
- Collect a blood sample of approximately 50 mL for immunogenicity assessments.
- Review the participant's e-diary data and collect the e-diary. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Record nonstudy vaccinations and concomitant medications as described in Section 6.5.3.
- Record AEs as described in Section 8.3.
- Complete the participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.11.3. Visit 3 – 6-Month Telephone Call Follow-up Visit (160-200 Days After Visit 1)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.
- Record nonstudy vaccinations and concomitant medications as described in Section 6.5.3.
- Record MAEs and SAEs as described in Section 8.3.
- Complete the participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.11.4. Unscheduled Visits

If the participant reports redness or swelling at the injection site measuring >20 measuring device units (>10.0 cm), fever ≥102.1°F (≥39.0°C), or severe injection site pain, severe nausea/vomiting, severe diarrhea, severe headache, severe fatigue, severe muscle pain, or severe joint pain, a telephone contact must occur as soon as possible between the participant and the investigator or a medically qualified member of the study site staff to assess if an

unscheduled visit is required. A site visit must be scheduled as soon as possible to assess the extent of the reaction unless:

- The participant is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the telephone contact, or
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error), or
- The investigator determined it was not needed.

This telephone contact will be recorded in the CRF and in the participant's source documentation.

If the participant is unable to attend the unscheduled visit, any ongoing reactions must be assessed at the next scheduled visit (Visit 2 and/or Visit 3).

The reactions should be assessed by the investigator or a medically qualified member of the study staff, such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure oral temperature.
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess any injection site pain that is present in accordance with the grading scale provided in Section 8.2.2.
- Assess any systemic events (nausea/vomiting, diarrhea, headache, fatigue, muscle pain, or joint pain) that are present in accordance with the grading scale provided in Section 8.2.2.

The investigator or an authorized designee will complete the unscheduled visit page of the CRF.

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 contact the participant to obtain additional information on Grade 3 events entered into the e-diary. Lastly, participants will be instructed to contact the site to report any significant illness, medical event, or hospitalization that occurs during the study period. The site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Statistical Hypotheses

There are no statistical hypotheses defined in the study.

9.1.2. Estimands

Primary (Safety):

In participants receiving at least 1 dose of the investigational product:

- The proportion of participants reporting prompted local reactions within 7 days following investigational product administration.
- The proportion of participants reporting prompted systemic events within 7 days following investigational product administration.
- The proportion of participants reporting AEs through 1 month following investigational product administration.
- The proportion of participants reporting MAEs and SAEs through 6 months following investigational product administration.

Missing e-diary data will not be imputed; missing AE dates and missing AE severity will be handled according to Pfizer safety rules.

Primary (Immunogenicity):

In participants receiving all doses of the investigational products 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–filamentous hemagglutinin (anti-FHA) antibodies from the GBS6+Tdap group to the placebo+Tdap group measured 1 month after vaccination.

- GMR, estimated by the GMR of antipertactin (anti-PRN) antibodies from the GBS6+Tdap group to the placebo+Tdap group measured 1 month after vaccination.

- GBS capsular polysaccharide (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.

These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed, as missing completely at random (MCAR) is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or violation observations will be censored.

Secondary

Not applicable.

Exploratory

In participants receiving all doses of the investigational products 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 ≥0.1 IU/mL measured 1 month after vaccination between the GBS6+Tdap group and the placebo+Tdap group.

- Geometric mean concentrations (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.

- Geometric mean fold rises (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.

- GBS capsular polysaccharide (CPS) serotype-specific IgG GMCs measured before and 1 month after vaccination for both the GBS6+Tdap group and the GBS6+placebo group.

- GBS capsular polysaccharide (CPS) serotype-specific IgG GMFRs measured from before vaccination to 1 month after vaccination for both GBS6+Tdap group and GBS6+placebo group.

9.2. Sample Size Determination

The study sample sizes are not based on any formal statistical hypothesis test considerations. The study aims to have a sufficient number of participants in order to describe the safety and immunogenicity of concomitantly administered Tdap and GBS6. With approximately 100 participants to be enrolled in each group, the lower bound of the 2-sided 95% CI for the 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, is approximately 0.40, 0.38, 0.53, 0.48, 0.63, and 0.46, assuming that there was no inherent difference between these 2 groups, and the maximum SD (natural logarithm scale) is 3.09, 3.27, 2.15, 2.48, 1.58, and 2.65 for serotypes Ia, Ib, II, III, IV, and V, respectively, from Study C1091001, with a 10% nonevaluable rate.

With a similar assumption of no inherent difference between groups, a similar nonevaluable rate, and 100 enrolled participants in each group, the lower bound of the 2-sided 95% CI for the GMR, estimated by the GMR of anti–pertussis toxin antibodies, anti-FHA antibodies, or anti-PRN antibodies from the GBS6+Tdap group to the placebo+Tdap group measured 1 month after vaccination, is approximately 0.74, 0.78, and 0.72, assuming maximum SDs (natural logarithm scale) of 1.01, 0.85, and 1.12 for anti–pertussis toxin antibody, anti-FHA antibody, anti-PRN antibody endpoints, respectively, and the lower bound of the 2-sided 95% CI for the difference in proportions of participants with anti–tetanus toxoid antibody concentrations ≥0.1 IU/mL and 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 is approximately -0.05 and -0.076, respectively, assuming that the proportions are 0.99 and 0.94 for anti–tetanus toxoid antibody and anti–diphtheria toxoid antibody endpoints from Study B1971015.

The primary safety objective includes the endpoints for local reactions, systemic events, AEs, MAEs, and SAEs.

Table 4 shows the probability of detecting at least 1 event (local reactions, systemic events, AEs, MAEs, or SAEs). The number of participants in each study group is 100, which provides a >86% chance of observing at least 1 event in a group, assuming a true rate of at least 2%.

Table 4. Probability of Observing at Least 1 Event by Assumed True Event Rates

Assumed True Event Percentage	Probability
0.10%	9.52%
0.50%	39.4%
1.0%	63.4%
2.0%	86.7%
3.0%	95.2%
4.0%	98.3%
5.0%	99.4%

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants who are assigned a randomization number in the IWR system.
Evaluable	All participants who are eligible, receive all doses of the investigational products to which they were randomized, have blood drawn for assay testing within the specified time frame for 1 month after vaccination, have at least 1 valid and determinate assay result at the 1-month postvaccination visit, and have no major protocol violations.
Modified intent-to-treat (mITT)	All randomized participants who receive at least 1 dose of the investigational products and have at least 1 valid and determinate assay result after vaccination.
Safety	All participants who receive at least 1 dose of the investigational products and have at least 1 valid postdose assessment.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	• Point estimates and exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (local reactions, systemic events, AEs, MAEs, and SAEs) for each vaccine group. • AEs and SAEs will be categorized according to MedDRA terms. A 3-tiered approach will be used to summarize AEs. For both Tier 1 and Tier 2 events, 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 test statistic proposed by Miettinen and Nurminen. 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. There are no preidentified Tier 1 events for this study. A MedDRA preferred term is defined as a Tier 2 event if there are 1% of 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. The safety analyses are based on the safety population. Participants will be summarized according to the vaccine group corresponding to the investigational product they actually received. Missing e-diary data will not be imputed; missing AE dates and missing AE severity will be addressed using the Pfizer safety rules.
Secondary	• N/A
Exploratory	• N/A

9.4.2. Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Primary	• The differences (GBS6+Tdap group minus placebo+Tdap group) in proportions of participants with anti–tetanus toxoid and 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 • 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 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 (2)-sided 95% CIs will also be obtained by calculating CIs using Student's t distribution for the mean

Endpoint	Statistical Analysis Methods
	difference of measures on the logarithmically transformed assay results and transforming confidence limits back to the original units. • GBS6 serotype-specific IgG GMR of the GBS6+placebo group to the GBS6+Tdap group at 1 month after vaccination will be calculated, along with associated 2-sided 95% CIs, using the same method as for anti–pertussis toxin, anti-FHA, and anti-PRN antibody GMRs. CCI [redacted] This analysis is based on the evaluable population. An additional analysis will be performed based on the mITT population if there is enough difference 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.
Exploratory	• 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 ≥0.1 IU/mL at each available time point for the GBS6+Tdap and placebo+Tdap groups. • 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 ≥1.0 IU/mL at each available time point for the GBS6+Tdap and placebo+Tdap groups. • 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 measured at each available time point after vaccination will be calculated and associated 2-sided 95% CIs will be calculated using the Miettinen and Nurminen method. • Geometric mean concentrations (GMCs) of anti-TTd, anti-DTd, anti–pertussis toxin, anti-FHA, anti-PRN, and anti-FIM antibodies at each available time point will be descriptively summarized for the GBS6+Tdap and placebo+Tdap groups, along with associated 2-sided 95% CIs. The GMC will be calculated as the mean of the antibody titers after the logarithm transformation and then transformed back to its original scale. Two (2)-sided 95% CIs will be constructed by calculating a CI for the mean of the logarithmically transformed assay results computed based on Student's t distribution and transforming confidence limits back to the original units.

Endpoint	Statistical Analysis Methods
	• Geometric mean fold rises (GMFRs) from before vaccination to each available time point after vaccination will be provided for anti-TTd, anti-DTd, anti–pertussis toxin, anti-FHA, anti-PRN, and anti-FIM antibodies for both the GBS6+Tdap and placebo+Tdap groups, along with associated 2-sided 95% CIs. The GMFR will be calculated as the mean of the difference of logarithmically transformed antibody titers (postvaccination minus prevaccination for each participant) and transformed back to the original units. Two (2)-sided 95% CIs will be computed by calculating CIs for the mean difference of measures on the logarithmically transformed assay results using Student's t distribution and transforming back to the original units. • GBS capsular polysaccharide (CPS) serotype-specific IgG GMCs at each available time point will be descriptively summarized for the GBS6+Tdap and GBS6+placebo groups, along with associated 2-sided 95% CIs, using the same method as for anti-TTd, anti-DTd, anti–pertussis toxin, anti-FHA, anti-PRN, and anti-FIM antibody GMCs. • GBS capsular polysaccharide (CPS) serotype-specific IgG GMFRs from before vaccination to each available time point after vaccination will be provided, for both the GBS6+Tdap and GBS6+placebo groups, along with associated 2-sided 95% CIs using the same method as for anti-TTd, anti-DTd, anti–pertussis toxin, anti-FHA, anti-PRN, and anti-FIM antibody GMFRs. • GBS capsular polysaccharide (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. • Point estimates and the exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportions of participants with serotype-specific GBS-positive vaginal/rectal cultures at each available time point for all 3 groups. IgG antibody concentrations denoted as BLQ will be imputed as 0.5 × LLOQ for GMC and GMT analyses, respectively. The above analyses are based on the evaluable population. An additional analysis will be performed based on the mITT population if there is enough difference 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.

9.5. 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.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

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

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC 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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about her right to access and correct her personal data and to withdraw consent for the processing of her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The definition of what constitutes source data can be found in ISF, which is maintained by the sponsor.

Description of the use of computerized systems is documented in the data management plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the ISF.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with an emergency contact card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available.

The ECC is intended to augment, but not replace, the established communication pathways between the investigator, site staff, and the study team. The ECC is to be used by healthcare professionals not involved in the research study, only as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

If an event is not an AE per definition above, 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).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

An SAE is defined as any untoward medical occurrence that, at any dose:
Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious • The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.
g. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Medically Attended Adverse Event

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

10.3.4. Definition of Immediate Adverse Event

Immediate AEs, defined as AEs occurring within the first 30 minutes after study intervention administration.

10.3.5. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with exposure during pregnancy or breastfeeding. **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE).* All instances of EDB are reported (whether or not there is an associated SAE).**
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* EDP (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.

AE and SAE Recording/Reporting

** EDB is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.

*** Environmental or occupational exposure: AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Intensity

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

Assessment of Causality
• The causality assessment is one of the criteria used when determining regulatory reporting requirements. • If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.6. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available.

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.2).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.2. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.3. Contraception Methods

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 2 (11 April 2022)

Overall Rationale for the Amendment: Study sample size and statistical analyses have been modified based on a strategic decision to describe the safety and immunogenicity in nonpregnant women, with a plan for a future study to evaluate the safety and immunogenicity in pregnant women.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis Section 2: Introduction Section 2.1: Study Rationale Section 2.2.2: Maternal Immunization as an Approach to Prevent Disease in Infants and Pregnant Women Section 2.3.1: Risk Assessment Section 3: Objectives, Estimands, and Endpoints Section 4.1: Overall Design Section 4.3: Justification for Dose Section 5.2: Exclusion Criteria Section 6.5.3: Recording Nonstudy Vaccinations and Concomitant Medications Section 9.1.1: Statistical Hypotheses Section 9.1.2: Estimands Section 9.2: Sample Size Determination Section 9.4.2: Immunogenicity Analyses	• Modified the primary immunogenicity objective and estimands to align with strategic decision of evaluating the immunogenicity interference with coadministration of Tdap and GBS6. • Revised the study sample size to align with modified safety and immunogenicity objective. • Modified the hypothesis-based noninferiority testing analysis for the primary immunogenicity endpoints to descriptive analysis due to the change in the primary study immunogenicity objective. • Modified appropriate statistical sections due to updates to the	• The study aims to have a sufficient number of participants in order to describe the safety and immunogenicity of coadministration of GBS6 and Tdap. • The study design is descriptive in nature, and descriptive statistics will be provided for the primary safety and primary immunogenicity endpoints.

Section # and Name	Description of Change	Brief Rationale
	primary immunogenicity objectives and estimands.	
Section 1.1: Synopsis Section 1.3: Schedule of Activities Section 2.3.3: Overall Benefit/Risk Conclusion Section 3: Objectives, Estimands, and Endpoints Section 7.2: Participant Discontinuation/Withdrawal From the Study Former Section 8.1.3: GBS Microbiological Cultures Section 8.1.3: Biological Samples Section 8.11.1: Visit 1 – Vaccination (Day 1) Section 8.11.2: Visit 2 – 1-Month Follow-up Visit (28-38 Days After Visit 1)	• Removed swabs for GBS microbiological cultures.	• Due to the reduction in study participants, there is no added value in taking the microbiological cultures.
Section 1.1: Synopsis Section 1.3: Schedule of activities Section 3: Objectives, Estimands, and Endpoints Section 4.1: Overall Design Section 6.5.3: Recording Nonstudy Vaccinations and Concomitant Medications Section 8.1: Efficacy and/or Immunogenicity Assessments Section 8.3.1: Time Period and Frequency for Collecting AE and SAE Information Former Section 8.11.3: Visit 3 – 6-Month Telephone Call Follow-up Visit (160-200 Days After Visit 1) Section 9.1.2: Estimands	• Modified the study follow-up period for participants to approximately 1 month after vaccination to align with the study objectives.	• Safety will be assessed through 1 month after vaccination. Immune responses to GBS6 and Tdap antigens will be measured 1 month after vaccination.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1: GBS Vaccine Antibody Testing Section 8.1.2: Tdap Antibody Testing	• Added an unblinded statistician who will identify participants from the dose groups.	• The addition of an unblinded statistician will allow study participants to be divided by immunogenicity assessment in order to decrease the number of assays required to be analyzed.
Document History Section 5.2: Exclusion Criteria Section 5.3.1: Contraception Section 5.5: Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration of Study Intervention Section 6: Study Intervention(s) and Concomitant Therapy Section 7.2.1: Withdrawal of Consent Section 8.2.5: Pregnancy Testing Section 8.3: Adverse Events and Serious Adverse Events Section 8.3.1: Time Period and Frequency for Collecting AE and SAE Information Section 8.3.5: Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure Section 10.1.3: Informed Consent Process Section 10.1.7: Source Documents Section 10.1.10: Sponsor's Qualified Medical Personnel Section 10.3.2: Definition of an SAE Section 10.3.5: Recording/Reporting and Follow-up of AEs and/or SAEs	• Updated wording to match mandatory text from the new protocol template.	• These changes were incorporated to align with the protocol template changes.

Section # and Name	Description of Change	Brief Rationale
Section 10.6: Appendix 6: Protocol Amendment History		

Amendment 1 (22 January 2021)

Overall Rationale for the Amendment: The GBS6 dose formulation has been updated to remove $AlPO_4$ since interim data from Study C1091002 show acceptable immune responses were achieved with the formulation that did not contain $AlPO_4$.

Section # and Name	Description of Change	Brief Rationale
Section 1 Section 4.1 Section 4.3 Section 6.1	The GBS6 dose formulation has been updated to remove $AlPO_4$	The GBS6 dose formulation has been updated to remove $AlPO_4$ since interim data from Study C1091002 shows acceptable immune responses were achieved with the formulation that did not contain $AlPO_4$.

10.7. Appendix 7: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
ADE	adverse device effect
AE	adverse event
$AlPO_4$	aluminum phosphate
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
CBER	Center for Biologics Evaluation and Research (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
CPS	capsular polysaccharide
CRF	case report form
CRM_{197}	cross-reactive material 197
CRO	contract research organization
CSR	clinical study report
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DTd	diphtheria toxoid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOD	early-onset disease
EU	European Union
EudraCT	European Clinical Trials Database
EU/mL	endotoxin units per milliliter
FDA	Food and Drug Administration (United States)
FHA	filamentous hemagglutinin
FIH	first-in-human
FIM	fimbriae
FSH	follicle-stimulating hormone
GBS	group B streptococcus

Abbreviation	Term
GBS6	group B streptococcus 6-valent polysaccharide conjugate vaccine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IAP	intrapartum antibiotic prophylaxis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IgG	immunoglobulin G
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
IU/mL	international units per milliliter
IWR	interactive Web-based response
Lf	flocculation units
LFT	liver function test
LLOQ	lower limit of quantitation
LMIC	low- and middle-income country
Ln	natural logarithm
LOD	late-onset disease
MAE	medically attended adverse event
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mIU/mL	milli-international units per milliliter
N/A	not applicable
NaCl	sodium chloride
PRN	pertactin
PT	prothrombin time
RCDC	reverse cumulative distribution curve
RSV	respiratory syncytial virus
SADE	serious adverse device effect

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
Td	tetanus and diphtheria vaccine
Tdap	tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine
TTd	tetanus toxoid
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
WOCBP	woman/women of childbearing potential

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Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
PPD	04-Oct-2022 14 45 29	Final Approval
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