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

Investigational Product Number:	CCI [redacted]
Investigational Product Name:	Group B Streptococcus 6-Valent Polysaccharide Conjugate Vaccine (GBS6)
United States (US) Investigational New Drug (IND) Number:	17058
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C1091007
Phase:	2

Short Title: A Phase 2 Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a Booster Dose of a Group B Streptococcus 6-Valent Polysaccharide Conjugate Vaccine (GBS6) in Healthy Adults

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	07 November 2019	Not applicable (N/A)

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Background and Rationale

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

This study is an extension to the completed first-in-human (FIH) C1091001 study and is to evaluate the safety and immunogenicity of a single booster vaccine dose of GBS6, administered approximately 2 years or more after a primary GBS6 dose, to healthy adult males and nonpregnant women. The study will determine whether individuals who received a primary dose of GBS6 have additional benefit following a booster dose. It will help assess if group B streptococcus (GBS) vaccination may be needed for each pregnancy.

Study Design

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

Healthy men and women will receive a single booster dose of GBS6 (20 μg) formulated with or without aluminum phosphate ($AlPO_4$) based on the formulation received in the primary C1091001 study. Participants will have blood drawn prior to vaccination (Visit 1) and 1 month after vaccination (Visit 2) and will receive a 6-month safety follow-up telephone call (Visit 3). Electronic diaries (e-diaries) will be used to collect prompted local reaction and systemic event data for 14 days after vaccination (Days 1 through 14, where Day 1 is the day of vaccination). Adverse events (AEs) (including medically attended adverse events [MAEs] and serious adverse events [SAEs]) will be collected through Visit 2 and MAEs and SAEs through Visit 3.

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

Number of Participants

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

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary (Safety):	**Primary (Safety):**	**Primary (Safety):**
• To describe the safety and tolerability of a single booster vaccination of GBS6 in healthy adults.	In participants receiving at least 1 dose of investigational product: • The proportion of participants reporting prompted local reactions within 14 days following investigational product administration. • The proportion of participants reporting prompted systemic events within 14 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.	• 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.

Secondary (Immunogenicity):	Secondary (Immunogenicity):	Secondary (Immunogenicity):
• To describe the immunogenicity for all vaccine serotypes after a single booster vaccination of GBS6. • To describe the immunogenicity for all vaccine serotypes after a single booster vaccination of GBS6 by baseline immunoglobulin G (IgG) geometric mean concentrations (GMCs) prior to the primary vaccination.	In participants in compliance with the key protocol criteria (evaluable population): • GBS serotype-specific IgG GMCs measured before and 1 month after booster vaccination. GBS serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) measured before and 1 month after booster vaccination. • GBS serotype-specific IgG geometric mean fold rise (GMFR) from before to 1 month after booster vaccination. • GBS serotype-specific OPA GMFR from before to 1 month after booster vaccination. • GBS serotype-specific IgG GMCs measured 1 month after booster vaccination stratified by baseline prevaccination status (before the primary vaccination).	• GBS serotype-specific IgG GMCs. • GBS serotype-specific OPA GMTs. • GBS serotype-specific IgG GMFRs. • GBS serotype-specific OPA GMFRs.

Investigational Product

The investigational product is GBS6 (20 μg capsular polysaccharide [CPS]/serotype/dose, formulated with or without $AlPO_4$), composed of CPS of serotypes Ia, Ib, II, III, IV, and V, individually conjugated to cross-reactive material 197 (CRM_{197}). At Visit 1, participants will receive 1 dose of GBS6, formulated with or without $AlPO_4$, administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm.

Statistical Methods

This is a descriptive study and sample size is not based on statistical considerations.

Descriptive summary statistics will be provided for the safety and immunogenicity endpoints.

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

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 Telephone Call**
Visit Window (Days)[a]	**Day 1**	**28-38 Days After Visit 1**	**160-200 Days After Visit 1**
Obtain informed consent	X		
Assign participant number	X		
Record demography	X		
Record medical history	X		
Record vital signs[b]	X		
Perform physical examination	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	X
Review temporary delay criteria	X	X	
Review continued eligibility		X	X
Assign container number	X		
Obtain blood sample for immunogenicity assessment[e]	X (~50 mL)	X (~50 mL or ~150 mL)	
Administer investigational product	X		
Postvaccination observation (30 minutes) and assessment of immediate AEs	X		
Dispense e-diary, thermometer, and measuring device[f]	X		
Review and/or collect e-diary[g]		X	

Visit Number	1	2	3
Visit Description	**Vaccination**	**1-Month Follow-up Visit**	**6-Month Telephone Call**
Visit Window (Days)[a]	**Day 1**	**28-38 Days After Visit 1**	**160-200 Days After Visit 1**
Record AEs	X	X	
Record MAEs and SAEs	X	X	X

Abbreviations: e-diary = electronic diary; MAE = medically attended adverse event.

a. Day relative to the 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 medication taken to treat an adverse event will be recorded in the case report form.
d. The contraception check is an opportunity to confirm that contraception is used consistently and correctly through the required time period per protocol (3 months after vaccination).
e. All blood volumes are approximate. At Visit 2, an optional additional immunogenicity blood draw of approximately 100 mL will be collected from participants who provide supplemental consent.
f. Participants will record in an e-diary prompted reactogenicity events each evening for 14 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 to Day 14 following vaccination to determine if an unscheduled visit is required.
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

2.1. Indication

GBS6 is being developed for:

- Active immunization to prevent disease caused by GBS serotypes contained in the vaccine.

2.2. Study Rationale

2.2.1. Rationale for Development of GBS6

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 GBS6 offers benefits beyond the currently 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 GBS6 for 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.

This study is an extension to the completed FIH C1091001 study and is to evaluate the safety and immunogenicity of a single booster vaccine dose of GBS6, administered approximately 2 years or more after a primary GBS6 dose, to healthy adult males and nonpregnant women. The study will determine whether individuals who received a primary dose of GBS6 have additional benefit following a booster dose. It will help assess if GBS vaccination may be needed for each pregnancy.

2.3. Background

2.3.1. 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 polysaccharide composition of their capsule. All GBS serotypes may cause disease, but there is 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 to it.[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 manifestation of GBS infection in older nonpregnant adults.[6,11,12]

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

The goal of maternal immunization is to boost maternal levels of specific antibodies to provide the newborn and young infant with sufficient IgG antibody concentrations at birth to protect them against infections occurring during a period of increased vulnerability, until they are able to adequately respond to their own active immunizations or infectious challenges. Examples of this concept include passive maternal antibody protection against tetanus, pertussis, respiratory syncytial virus (RSV), influenza virus, and GBS infections, among others.[13]

Vaccination of pregnant women is used globally in the prevention of neonatal tetanus and more recently for prevention of 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 of the world to prevent disease in newborns and infants. Maternal immunization against influenza is recommended by the US Advisory Committee on Immunization Practices (ACIP).[18,19,20,21] To date, these vaccines have demonstrated an acceptable safety profile with single and repeat dosing during every pregnancy, including closely spaced pregnancies.[22,23,24]

Current preventive measures against invasive GBS disease in infants in some high-income countries, such as the United States, 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. This approach has been highly effective against early-onset disease (EOD), which occurs within the first week of life, but has not been effective in reducing rates of late-onset disease (LOD), which occurs between Days 7 and 90, and is not implemented globally because of the high resource burden.[25,26,27] Additionally, GBS disease in pregnant and postpartum women has not been reduced,[28] as may be expected given the short course of administration during the intrapartum period only. In other countries where interventions are less widely used or a risk-based approach to IAP is used, such as in certain European countries, the trend in incidence rates may be unchanged or increasing slightly.[7,29] Neither approach has eliminated GBS disease in infants. Finally, widespread use of IAP confers the potential for antibiotic resistance and may have short- and long-term impact on the infant microbiome.[30] Immunization of pregnant women with a GBS vaccine is a reasonable alternative approach to prevent invasive GBS disease in young infants and possibly GBS disease in pregnant or postpartum women.[31]

2.3.3. Maternal Antibody and Protection Against GBS Disease in Infants

During the third trimester of pregnancy, only IgG antibodies are actively transported across the placenta. This provides a means for protective antibody to be transferred from a mother to her newborn.[32] The efficiency of antibody transfer depends on placental integrity, maternal total IgG, gestational age at delivery, and IgG subclass (IgG1 subclass is most efficiently transferred).[16] Researchers measured antibody in sera collected at delivery from GBS-colonized mothers whose infants had developed EOD, and in GBS-colonized women whose infants had not developed EOD. was a correlation between low maternal antibody

concentration to serotype III (as measured in an IgG assay) and infant susceptibility to EOD due to serotype III.[33] Since the initial study, additional work was conducted demonstrating the correlation between serotype Ia–specific anti-CPS antibody in the mother and protection of the baby against GBS EOD due to serotype Ia, and a directional effect with the serotype V antibody.[3,34,35,36] This suggests that anti-CPS antibody protects against GBS disease, a mechanism similar to that exploited against other encapsulated organisms, and the antibody is transported across the placenta. These findings support the biological plausibility that increasing the levels of maternal anti-CPS IgG antibody by vaccination of pregnant women with serotype-specific polysaccharide conjugate antigens will increase the proportion of women with potentially protective levels of IgG and will result in placental transfer of protective antibody to a large number of infants.[37,38]

2.3.4. Clinical Experience With Polysaccharide Conjugate Vaccine and GBS Polysaccharide Conjugate Vaccine

There is significant experience with the use of polysaccharide conjugate vaccines to prevent disease due to encapsulated bacteria in infants, children, and adults.[39,40] A number of polysaccharide conjugate vaccines have been developed and globally licensed by Pfizer (HibTITER®, Meningitec®, Prevnar®, Prevnar 13®) and other vaccine manufacturers (eg, Menveo, ActHib, Hiberix). These vaccines have a well-established safety profile and induce high levels of functionally active antibodies that are protective as demonstrated either through efficacy studies or based on established immune correlates of protection. GBS6 was developed based on Pfizer experience with licensed and investigational polysaccharide conjugate vaccines, published/public data with other investigational GBS polysaccharide conjugate vaccines, and data from the preclinical models of GBS6.[41,42,43,44,45,46,47,48,49,50] Investigational GBS polysaccharide conjugate vaccines were evaluated in clinical trials in pregnant women, including a trivalent (Ia, Ib, and III) GBS CPS–CRM197 conjugate vaccine in South Africa.[51,52] These studies demonstrated the acceptable safety profile of GBS polysaccharide conjugate vaccines, as well as the induction of immune responses to the GBS vaccine serotypes in their infants.

GBS6 was evaluated in a Phase 1/2 FIH study in healthy nonpregnant women and men 18 through 49 years of age in the United States. 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 serotype IgG immune response was observed 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.[51,53,54,55]

2.3.5. Clinical Experience With Repeated Doses of Vaccines

There is precedent for repeated doses of vaccines to augment or sustain protection against disease in pregnant women. Several countries recommend tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap) during every pregnancy, including closely spaced pregnancies. Published data report that vaccination with Tdap during pregnancy is not associated with an increased risk of adverse pregnancy outcomes[21] and suggest that repetitive

dosing in a short time span in serial pregnancies does not unfavorably affect pregnancy. In one study no adverse pregnancy, delivery, or neonatal outcomes were observed in association with antepartum Tdap vaccination in women who received more than 1 antepartum Tdap vaccinations spaced in a 5-year time frame.[56]

Data are available regarding boosting of IgG responses from Phase 1 and 2 clinical trials of other GBS candidate vaccines. In one study, a second dose of an investigational trivalent GBS vaccine, administered 4 to 6 years after the first dose, elicited a robust immune response for each vaccine serotype in nonpregnant women, including in those with undetectable pre–first dose anti-GBS antibody levels. The authors suggest a sufficiently spaced second vaccine dose may be beneficial for women with very low preexisting antibody concentrations.[57] In another study investigating a different GBS candidate vaccine, a second dose of GBS III-TT vaccine given 21 months after the first dose restored type III CPS-specific IgG antibody levels to those obtained after the primary vaccination. The ability of a second dose to augment the immune response was apparent only in the subset of healthy adults who had very low concentrations (<0.05 µg/mL) of CPS-specific IgG prior to vaccination. In this group, the second dose resulted in specific IgG GMCs that were 3-fold higher than that obtained after a single dose.[58] These data suggest that repeat vaccination is safe and may offer immunologic benefit.

The purpose of this Phase 2, open-label study is to determine whether a single booster dose of GBS6 given to healthy adults approximately 2 years or more after receipt of their initial dose in the GBS6 Phase 1/2 FIH study is safe and can elicit serotype-specific immune responses.

2.4. 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,[1,2] individually conjugated to the CRM_{197} carrier protein. An efficacious vaccine would offer a favorable alternative 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 the CPS and generate functional antibodies that eliminate bacteria by opsonophagocytosis.

A recently 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 single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary (Safety):	**Primary (Safety):**	**Primary (Safety):**
• To describe the safety and tolerability of a single booster vaccination of GBS6 in healthy adults.	In participants receiving at least 1 dose of investigational product: • The proportion of participants reporting prompted local reactions within 14 days following investigational product administration. • The proportion of participants reporting prompted systemic events within 14 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.	• 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.

Secondary (Immunogenicity):	Secondary (Immunogenicity):	Secondary (Immunogenicity):
• To describe the immunogenicity for all vaccine serotypes after a single booster vaccination of GBS6. • To describe the immunogenicity for all vaccine serotypes after a single booster vaccination of GBS6 by baseline IgG GMCs prior to the primary vaccination.	In participants in compliance with the key protocol criteria (evaluable population): • GBS serotype-specific IgG GMCs measured before and 1 month after booster vaccination. • GBS serotype-specific OPA GMTs measured before and 1 month after booster vaccination. • GBS serotype-specific IgG GMFR from before to 1 month after booster vaccination. • GBS serotype-specific OPA GMFR from before to 1 month after booster vaccination. • GBS serotype-specific IgG GMCs measured 1 month after booster vaccination stratified by baseline prevaccination status (before the primary vaccination).	• GBS serotype-specific IgG GMCs. • GBS serotype-specific OPA GMTs. • GBS serotype-specific IgG GMFRs. • GBS serotype-specific OPA GMFRs.

4. STUDY DESIGN

4.1. Overall Design

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

Healthy men and women will receive a single booster dose of GBS6 (20 μg) formulated with or without $AlPO_4$ based on the formulation received in the primary C1091001 study; ie, participants who received 5 μg, 10 μg, or 20 μg without $AlPO_4$ in C1091001 will receive 20 μg without $AlPO_4$. Participants who received 5 μg, 10 μg, or 20 μg with $AlPO_4$ in C1091001 will receive 20 μg with $AlPO_4$.

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

An E-DMC will be utilized.

4.1.1. Approximate Duration of Participation of Each Participant

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

4.1.2. Approximate Number of Participants

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

4.2. Scientific Rationale for Study Design

Refer to Section 2.2

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).

The FIH study was conducted in healthy nonpregnant women and healthy men in the United States 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 with or without $AlPO_4$) is selected for this study as it represents the greatest challenge in terms of acceptable safety of a second dose and potentially maximizes immune response.

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. Male or female participants. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

- Participants who were 18 through 49 years of age at the time of enrollment in the C1091001 study.

Type of Participant and Disease Characteristics:

2. Participants who were enrolled in the C1091001 study, received GBS6, and completed the 1-month blood draw. *Note:* Participants who withdrew from the C1091001 study after the 1-month blood draw are eligible for participation if no exclusion criteria apply.

3. 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 14 following administration of investigational product.

4. Healthy adults (male and female) at enrollment who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

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

Informed Consent:

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (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 fertile men 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 3 months after the last dose of investigational product.

Medical Conditions:

2. Any prior history (including the interval after completion of the C1091001 study) 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. Any prior history (including the interval after completion of the C1091001 study) of microbiologically proven invasive disease caused by GBS (*S agalactiae*).

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 acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study. Chronic medical conditions including human immunodeficiency virus (HIV), chronic hepatitis B virus (HBV) infection (HBV surface antigen positive), and/or hepatitis C virus infection.

Prior/Concomitant Therapy:

7. Previous vaccination with any licensed or investigational GBS vaccine (other than GBS6 received in Study C1091001), or planned receipt during the participant's participation in the study (through the 6-month postvaccination telephone call).

8. 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 6-month postvaccination telephone contact. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 30 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

9. Vaccination with diphtheria- or CRM_{197}-containing vaccine(s) within 6 months before investigational product administration, or planned receipt through the 1-month postvaccination blood draw visit.

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

Prior/Concurrent Clinical Study Experience:

11. 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:

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

5.2.1. 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).

5.2.1.1. Criteria for Temporarily Delaying Vaccine Administration

- Current febrile illness (body temperature ≥100.4ºF [≥38.0ºC]) 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.

5.2.1.2. Criteria for Temporarily Delaying Blood Draw

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

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 his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) 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). 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 entered in the study through assignment of investigational product. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

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

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(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 product is GBS6 (20 µg CPS/serotype/dose, formulated with or without $AlPO_4$).

6.1.1. GBS6

GBS6 is composed of serotypes Ia, Ib, II, III, IV, and V CPS CCI [redacted] There is 1 dose level (20 µg CPS/serotype/CCI [redacted] formulated either with $AlPO_4$, CCI [redacted] or without $AlPO_4$. See Table 1 for further details.

CCI [redacted]

CCI [redacted]

[redacted]

6.1.2. Administration

Participants will receive 1 dose of GBS6, with or without $AlPO_4$, at Visit 1 in accordance with the study's SoA.

GBS6 should be administered intramuscularly by injecting 0.5 mL into the deltoid muscle.

CCI [redacted]

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 investigational products should be performed by an appropriately qualified, Good Clinical Practice (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.

Investigational product administration details will be recorded on the case report form (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, as applicable for temperature-monitored shipments.

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 temperature since previously documented for all site storage locations upon return to business.

4. The investigator, the 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). All study interventions will be accounted for using an investigational product accountability form/record.

5. Further guidance and information for the final disposition of unused study interventions CCI [redacted].

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

7. Study interventions should be stored in their original containers and in accordance with the labels.

8. 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. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. 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.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). 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, and all destruction must be adequately documented.

CCI [redacted]

6.2.1. Preparation and Dispensing

CCI [redacted] Investigational product should be prepared and dispensed by an appropriately qualified and experienced 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 Investigational Product

This is an open-label study; however, the specific investigational product dispensed to the participant will be assigned using an interactive response technology (IRT). Participants will receive 1 dose of GBS6 (20 µg CPS/serotype/dose, formulated with or without $AlPO_4$). $AlPO_4$ allocation will be consistent with the C1091001 study. The site will contact the IRT prior to the start of investigational product administration for each participant. The site will record the investigational product assignment on the applicable CRF.

The investigator's knowledge of the investigational product should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Investigational product will be dispensed at the study visits summarized in the SoA.

The study-specific IRT reference guide 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 starting 15 days after investigational product administration. If medically necessary (eg, pandemic), influenza vaccine 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, 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.

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 8.5.1).

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

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, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

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 him or her.

At the time of discontinuing from the study, please refer to the investigator site file (ISF) and the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) 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 Clinical Trial (CT) SAE Report.

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.

Withdrawal of Consent:

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 him or her. 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 study procedures (eg, blood draw) and/or postvaccination study safety

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 he or 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:

- 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, he/she will be considered to have withdrawn from the study.

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.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

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.

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

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if 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 or 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. Study Procedures

8.1.1. 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.
- 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).
- Prior to vaccination, perform a urine pregnancy test for WOCBP and ensure the result is negative.

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

- Verify the participant's understanding of and compliance with the protocol requirements for contraception. Instruct the participant to use appropriate contraceptives until 3 months after administration of investigational product and document the conversation and the participant's affirmation in the participant's source document.

- Obtain participant investigational product container number using the IRT system and prepare the investigational product. Please refer to the IP manual for further instruction on this process.

- Administer a single 0.5-mL injection of investigational product into the deltoid muscle [redacted]

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

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

- Issue the participant an e-diary and provide instructions on its completion. Ask the participant to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if he or she is prompted by the e-diary from Day 1 to Day 14 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring >20 measuring device units [>10 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 a medically attended event (eg, emergency room) or hospitalization occurs.

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

- Record nonstudy vaccinations and medications as described in Section 6.5.3.

- Record AEs as described in Section 8.5.

- Complete the participant's source documents.

- The investigator or an authorized designee completes the CRF and a 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.

8.1.2. 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 5.2.1.2.
- 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. Alternatively, for participants who have consented to participate, collect approximately 150 mL of blood.
- 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 8.5.
- Complete the participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.1.3. Visit 3 – 6-Month Telephone Call (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.
- Verify the participant's compliance with the protocol requirements for contraception.
- Record nonstudy vaccinations and concomitant medications as described in Section 6.5.3.
- Record AEs as described in Section 8.5.
- Complete the participant's source documents.
- The investigator or an authorized designee completes the CRF.

8.1.4. Unscheduled Visits

If the participant reports redness or swelling at the injection site measuring >20 measuring device units (>10 cm), fever ≥102.1°F (≥39.0°C), or severe injection site pain,

nausea/vomiting, diarrhea, headache, fatigue, muscle pain, or 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 8.4.2.
- Assess for lymphadenopathy associated with any present local reaction.
- 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 8.4.2.

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, joint pain) within 14 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.

8.2. Efficacy Assessments

Not applicable.

8.3. 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; or approximately 150 mL (an additional optional 100 mL) for those participants who consent to a larger blood draw at Visit 2. Sample collection, processing, storage, and shipping information can be found in the CCI [redacted]. Sera will be used for immunogenicity assessments, assay development, and routine assay maintenance.

OPA results for the 6 serotypes (Ia, Ib, II, III, IV, V) will be determined in all participants for each blood sample at Day 1 and at 1 month after vaccination. Results will be reported as OPA titers.

Concentrations of anticapsular IgG for the 6 serotypes (Ia, Ib, II, III, IV, V) will be determined in all participants for each blood sample at Day 1 and at 1 month after vaccination and reported as IgG concentrations.

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.

8.3.1. 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 his or 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.

8.4. 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 concerns.

8.4.1. Participant Electronic Diary

The participant will be asked to monitor and record local reactions, systemic events, including fever, and antipyretic/pain medication used to treat symptoms, each evening for 14 days following vaccination (Day 1 through Day 14, where Day 1 is the day of vaccination) on a system that uses a personal digital assistant (PDA) or other technology. 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, 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.

8.4.2. 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 Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[59]

8.4.2.1. Local Reactions

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

local reaction will be prompted to contact the investigator to perform an unscheduled visit and assess the reaction.

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 2. Local Reaction Grading Scale

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

a. Participants experiencing ≥ Grade 3 local reactions are to be seen by the study site. Refer to the Unscheduled Visits section 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.

8.4.2.2. Systemic Events

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

vaccination. Study staff may also contact the participant to obtain additional information on Grade 3 events entered into the e-diary.

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

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

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Grade 4[b]
Nausea/Vomiting	No interference with activity or 1-2 times in 24 hours	Some interference with activity or >2 times in 24 hours	Prevents daily activity; requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools in 24 hours	4-5 loose stools in 24 hours	≥6 loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity[c]	Emergency room visit or hospitalization for severe headache
Fatigue (= tiredness in diaries)	No interference with activity	Some interference with activity	Significant; prevents daily activity[c]	Emergency room visit or hospitalization for severe fatigue
Muscle pain	No interference with activity	Some interference with activity	Significant; prevents daily activity[c]	Emergency room visit or hospitalization for severe muscle pain

Table 3. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

a. Participants experiencing ≥ Grade 3 systemic events are to be seen by the study site. Refer to the Unscheduled Visits section 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.

8.4.2.3. 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 14 days following vaccination (Days 1 to 14, where Day 1 is the day of vaccination) and at any time during the 14 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 14, 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 >104.0°F (>40.0°C) will be prompted to contact the investigator to assess the fever and perform an unscheduled visit as appropriate. Study staff must also contact the participant to obtain additional information if a temperature of >102.0°F is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 4:

Table 4. Ranges for Fever

100.4°F to 101.1°F (38.0°C to 38.4°C)
101.2°F to 102.0°F (38.5°C to 38.9°C)
102.1°F to 104.0°F (39.0°C to 40.0°C)
>104.0°F (>40.0°C)

8.4.3. Use of Antipyretic/Pain Medication

From Day 1 to Day 14, 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.

8.4.4. Clinical Safety Laboratory Assessments

Not applicable.

8.4.5. Pregnancy Testing

Urine pregnancy tests will 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 administration of the vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the investigational product. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy *after* administration of investigational product, the participant may remain in the study for blood sample collection and safety monitoring.

8.5. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 it meets the criteria for classification as an SAE or that caused the participant to discontinue from the study (see Section 7).

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

8.5.1. 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 investigational product), through and including Visit 2 (1 month after vaccination) for AEs and through and including Visit 3 for MAEs and SAEs.

AEs that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed or withdrawn early from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.5.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report 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.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.5.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.5.2. 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.

8.5.3. 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.

8.5.4. 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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

8.5.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.5.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 3 months after vaccination.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.5.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. 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's administration, the SAE is reported together with the exposure during breastfeeding.

8.5.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. 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 CT SAE Report Form is maintained CCI .

8.5.6. Medication Errors

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report 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 investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Other examples include, but are not limited to:

- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

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 immediately.

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 an AE page of the CRF.

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

8.6. 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 immediately.
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.**

8.7. Pharmacokinetics

Not applicable.

8.8. Pharmacodynamics

Not applicable.

8.9. Genetics

8.9.1. Specified Genetics

Not applicable.

8.9.2. Banked Biospecimens for Genetics

Not applicable.

8.10. Biomarkers

Not applicable.

8.11. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (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. Estimands

Primary (Safety):

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

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

Secondary (Immunogenicity):

In participants receiving at least 1 dose of the investigational product and in compliance with the key protocol criteria (evaluable participants):

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

- GBS serotype-specific IgG GMFR from before to 1 month after booster vaccination.
- GBS serotype-specific OPA GMFR from before to 1 month after booster 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. Participants who discontinue or have major protocol deviations before Visit 2 (1 month after receiving the investigational product) will be excluded from the evaluable population in the analysis. Immunogenicity results that are below the lower limit of quantitation (LLOQ) will be set to 0.5 × LLOQ in the analysis.

9.1.2. Statistical Hypotheses

There are no formal statistical hypotheses for this study.

9.2. Sample Size Determination

CCI [redacted]

In C1091001, 297 participants who received GBS6 completed the study. The study intends to enroll as many participants as possible who are eligible and willing to participate in the study. CCI [redacted]

[redacted]

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Evaluable immunogenicity	All participants who are enrolled and receive 1 dose of the investigational product, have Visit 2 blood collection within an appropriate window for Visit 2, have at least 1 valid and determinate assay result at Visit 2, and have no other major protocol deviations as determined by the clinician.
Modified intent-to-treat (mITT)	All participants who receive 1 dose of the investigational product and have at least 1 valid and determinate assay result after receiving the investigational product. Participants will be summarized according to the investigational product group to which they were assigned.
Safety	All participants who receive 1 dose of the investigational product and have safety data reported after receiving the investigational product. Participants will be summarized according to the investigational product they actually received.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in 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. Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable (N/A).
Secondary	• The serotype-specific IgG GMCs and OPA GMTs will be calculated as the mean of the logarithmically transformed assay results and then transformed back to the original units. The 2-sided 95% confidence intervals (CIs) will be constructed by obtaining CIs for the mean of the logarithmically transformed assay results using Student's t distribution and transforming the confidence limits back to the original units. • The serotype-specific IgG GMCs measured at 1 month after booster vaccination stratified by baseline prevaccination status (before the primary vaccination) will be calculated as the mean of the logarithmically transformed assay results and then transformed back to the original units. The 2-sided, 95% CIs will be constructed by obtaining CIs for the mean of the logarithmically transformed assay results using Student's t distribution and transforming the confidence limits back to the original units. • The serotype-specific GMFR from before to 1 month after the booster vaccination for both IgG and OPA will be calculated as the mean of the difference (postvaccination minus prevaccination) of the logarithmically transformed antibody titers and then transformed back to the original units. The 2-sided 95% CIs will be constructed by obtaining CIs for the mean of the differences of the logarithmically transformed assay results using 1-sample Student's t distribution and transforming the confidence limits back to the original units.

Endpoint	Statistical Analysis Methods
	• Empirical reverse cumulative distribution curves (RCDCs) will be presented graphically by plotting the proportion of participants with the GBS6 serotype-specific antibody level equal to or exceeding the specified antibody level versus the antibody level by vaccine group and at 1 month after vaccination for serotype-specific IgG concentration and OPA titers. Titers below the LLOQ or denoted as below the limit of quantitation (BLQ) will be set to 0.5 × LLOQ for GMT/GMC analysis. This analysis is based on the evaluable immunogenicity population. Immunogenicity analyses based on the mITT population will be performed if there is a 10% or more difference between the mITT population and the evaluable immunogenicity population.
CCI [redacted]	[redacted]

9.4.2. 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 percentage 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 Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tiered approach will be used to summarize AEs. There are no preidentified Tier 1 events for this study. A MedDRA preferred term is defined as a Tier 2 event if there are 4 or more participants in at least 1 vaccine group reporting the event. Descriptive summary statistics (counts and percentages) will be provided for Tier 2 events for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing e-diary data will not be imputed; missing AE dates and missing AE severity will be handled according to the Pfizer safety rules.
Secondary	Not applicable (N/A).
CCI [redacted]	[redacted]

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

9.5.1. Data Monitoring Committee

This study will use an E-DMC.

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

CCI [redacted]

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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, IB, 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 Code of Federal Regulations (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 investigational product, 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 to the participant and answer all questions regarding the study.

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, Health Insurance Portability and Accountability Act (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 his/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 his/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 his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or 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 shall 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 natural persons 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 his or her actual identity. 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 European Clinical Trials Database (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 standard operating procedures (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 US Basic 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. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report [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 US Basic Results document is 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 European Medicines Agency (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 contribute 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 electronic CRF (eCRF) that are transcribed 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.

Definition of what constitutes source data can be found in the ISF.

10.1.8. Study and Site Closure

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 contract research organization (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.

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 18 months after 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 supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. 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. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact

number is not intended for use by the participant directly, and if a participant calls that number, he or 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, electrocardiogram [ECG], radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from

lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

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 Immediate Adverse Event

Immediate AEs, defined as AEs occurring within the first 30 minutes after investigational product administration, will be assessed and documented in the AE CRF. The time of onset will be recorded for any AEs that occur on the same day as investigational product administration.

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 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.

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. 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.

10.3.5. 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 CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report 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 CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- 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 CT SAE Report 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/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.

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or 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/SAE.
- 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.

- The investigator will use clinical judgment to determine the relationship.
- 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.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" 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 CT SAE Report 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 professionals.
- 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.
- 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 CT SAE Report Form

- Facsimile transmission of the CT SAE Report 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 CT SAE Report 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 CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 3 months after the last dose of study intervention:

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in sexual activity with a WOCBP that could result in pregnancy.

- In addition to male condom use, a highly effective method of contraception is recommended in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. 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 10.4.3)

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 3 months 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.

10.4.3. Woman of Childbearing Potential (WOCBP)

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 age 60 years or older or no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
     - Females 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.

10.4.4. Contraception Methods

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

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

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 WOCBP 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;
    - injectable.

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).

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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).

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 includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

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.

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 drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (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 aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (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, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (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 (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 sample for acetaminophen 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: Abbreviations

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

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices (United States)
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
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
CT	clinical trial
DILI	drug-induced liver injury
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
FDA	Food and Drug Administration (United States)
FIH	first-in-human
FSH	follicle-stimulating hormone
GBS	group B streptococcus
GBS6	group B streptoccous 6-valent polysaccharide conjugate vaccine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
HBV	hepatitis B virus

Abbreviation	Term
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IAP	intrapartum antibiotic prophylaxis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LFT	liver function test
LLOQ	lower limit of quantitation
LMIC	low- and middle-income country
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
N/A	not applicable
NaCl	sodium chloride
OPA	opsonophagocytic activity
PCD	primary completion date
PDA	personal digital assistant
PT	prothrombin time
RCDCs	reverse cumulative distribution curves
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
Tdap	tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine
ULN	upper limit of normal
US	United States
WOCBP	woman of childbearing potential

11. REFERENCES

1 Madzivhandila M, Adrian PV, Cutland CL, et al. Serotype distribution and invasive potential of group B streptococcus isolates causing disease in infants and colonizing maternal-newborn dyads. PLoS One 2011;6(3):e17861.

2 Melin P, Efstratiou A. Group B streptococcal epidemiology and vaccine needs in developed countries. Vaccine 2013;31(Suppl 4):D31-42.

3 Lin FYC, Philips JB III, Azimi PH, et al. Level of maternal antibody required to protect neonates against early-onset disease caused by group B streptococcus type Ia: a multicenter, seroepidemiology study. J Infect Dis 2001;184(8):1022-8.

4 Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. JAMA 2008;299(17):2056-65.

5 Edmond KM, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet 2012;379(9815):547-56.

6 Skoff TH, Farley MM, Petit S, et al. Increasing burden of invasive group B streptococcal disease in nonpregnant adults, 1990-2007. Clin Infect Dis 2009;49(1):85-92.

7 Lamagni TL, Keshishian C, Efstratiou A, et al. Emerging trends in the epidemiology of invasive group B streptococcal disease in England and Wales, 1991-2010. Clin Infect Dis 2013;57(5):682-8.

8 Deutscher M, Lewis M, Zell ER, et al. Incidence and severity of invasive *Streptococcus pneumoniae*, group A *Streptococcus*, and group B *Streptococcus* infections among pregnant and postpartum women. Clin Infect Dis 2011;53(2):114-23.

9 Edwards MS, Nizet V, Baker CJ. Group B streptococcal infections. In: Remington JS, ed. Infectious diseases of the fetus and newborn. 7th Ed. Amsterdam, the Netherlands: Elsevier; 2011:419-69. Available from: http://dx.doi.org/10.1016/B978-1-4160-6400-8.00012-2. Accessed: 15 Sep 2015.

10 Baker CJ. The spectrum of perinatal group B streptococcal disease. Vaccine 2013;31(Suppl 4):D3-6.

11 Smith EM, Khan MA, Reingold A, et al. Group B streptococcus infections of soft tissue and bone in California adults, 1995-2012. Epidemiol Infect 2015;143(15):3343-50.

12 Natarajan P, Poretz DM. The increasing threat of group B *Streptococcus* infection in adults [abstract 738]. Open Forum Infect Dis 2014;1(Suppl 1):S208-9.

[13] Munoz FM. Current challenges and achievements in maternal immunization research. Front Immunol 2018;9:436.

[14] Berenson AB, Hirth JM, Rahman M, et al. Maternal and infant outcomes among women vaccinated against pertussis during pregnancy. Hum Vaccin Immunother 2016;12(8):1965-71. DOI:10.1080/21645515.2016.1157241.

[15] Swamy GK, Beigi RH. Maternal benefits of immunization during pregnancy. Vaccine 2015;33(47):6436-40.

[16] Englund JA. The influence of maternal immunization on infant immune responses. J Comp Pathol 2007;137(Suppl 1):S16-9.

[17] Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008:359(15):1555-64.

[18] Madhi SA, Cutland CL, Kuwanda L, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014;371(10):918-31.

[19] Harper SA, Fukuda K, Uyeki TM, et al; Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP) [erratum appears in MMWR Recomm Rep 2004;53(32):743]. MMWR Recomm Rep 2004;53(RR-6):1-40. Update appears in MMWR Recomm Rep 2005;54(RR-8): 1-40.

[20] Munoz FM, Bond NH, Maccato M, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA 2014;311(17):1760-9.

[21] Layton JB, Butler AM, Li D, et al. Prenatal Tdap immunization and risk of maternal and newborn adverse events. Vaccine 2017;35(33):4072-8.

[22] Lindsey B, Kampmann B, Jones C. Maternal immunization as a strategy to decrease susceptibility to infection in newborn infants. Curr Opin Infect Dis 2013;26(3):248-253.

[23] Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012. MMWR Morb Mortal Wkly Rep 2013;62(7):131-5.

[24] Australian Government Department of Health. Pertussis (whooping cough). In: Australian immunisation handbook. Available from: https://immunisationhandbook.health.gov.au/vaccine-preventable-diseases/pertussis-whooping-cough. Updated: 20 Sep 2019. Accessed: 24 Oct 2019.

[25] Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 2000;342(1):15-20.

[26] Puopolo KM, Lynfield R, Cummings JJ, AAP Committee on Fetus and Newborn, AAP Committee on Infectious Diseases. Management of infants at risk for group B streptococcal disease. Pediatrics 2019;144(2):e20191881.

[27] American College of Obstetricians and Gynecologists. ACOG committee opinion, number o.782: prevention of gGroup B streptococcal early- onset disease in newborns. Obstet Gynecol 2019;134(1):e19-40.

[28] Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep 2010;59(RR-10): 1-31.

[29] Bekker V, Bijlsma MW, van de Beek D, et al. Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in the Netherlands over 25 years: a nationwide surveillance study. Lancet Infect Dis 2014;14(11):1083-89.

[30] Seedat F, Stinton C, Patterson J, et al. Adverse events in women and children who have received intrapartum antibiotic prophylaxis treatment: a systematic review. BMC Pregnancy Childbirth 2017;17(1):247.

[31] Dzanibe S, Madhi SA. Systematic review of the clinical development of group B streptococcus serotype-specific capsular polysaccharide-based vaccines. Expert Rev Vaccines 2018;17(7):635-51.

[32] Palmeira P, Quinello C, Silveira-Lessa AL, et al. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol 2012;2012:985646.

[33] Baker CJ, Kasper DL. Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. N Engl J Med 1976;294(14):753-6.

[34] Baker CJ, Carey VJ, Rench MA, et al. Maternal antibody at delivery protects neonates from early onset group B streptococcal disease. J Infect Dis 2014;209(5):781-8.

[35] Baker CJ, Edwards MS, Kasper DL. Role of antibody to native type III polysaccharide of group B *Streptococcus* in infant infection. Pediatrics 1981;68(4):544-9.

[36] Lin FYC, Weisman LE, Azimi PH, et al. Level of maternal IgG antigroup B streptococcus type III antibody correlated with protection of neonates against early-onset disease caused by this pathogen. J Infect Dis 2004;190(5):928-34.

[37] Fabbrini M, Rigat F, Rinaudo CD, et al. The protective value of maternal group B streptococcus antibodies: quantitative and functional analysis of naturally acquired

responses to capsular polysaccharides and pilus proteins in European maternal sera. Clin Infect Dis 2016;63(6):746-53. DOI: 10.1093/cid/ciw377.

[38] Dangor Z, Kwatra G, Izu A. Correlates of protection of serotype-specific capsular antibody and invasive group B streptococcus disease in South African infants. Vaccine 2015;33(48):6793-9.

[39] Pichichero ME. Protein carriers of conjugate vaccines: characteristics, development, and clinical trials. Hum Vaccin Immunother 2013;9(12):2505-23.

[40] Gruber WC, Scott DA, Emini EA. Development and clinical evaluation of Prevnar 13, a 13-valent pneumococcal CRM_{197} conjugate vaccine. Ann N Y Acad Sci 2012;1263(1):15-26.

[41] Kasper DL, Paoletti LC, Wessels MR, et al. Immune response to type III group B streptococcal polysaccharide-tetanus toxoid conjugate vaccine. J Clin Invest 1996;98(10):2308-14.

[42] Heath PT. An update on vaccination against group B streptococcus. Expert Rev Vaccines 2011;10(5):685-94.

[43] Baker CJ, Rench MA, Fernandez M, et al. Safety and immunogenicity of a bivalent group B streptococcal conjugate vaccine for serotypes II and III. J Infect Dis 2003;188(1):66-73.

[44] Baker CJ, Rench MA, Paoletti LC, et al. Dose-response to type V group B streptococcal polysaccharide-tetanus toxoid conjugate vaccine in healthy adults. Vaccine 2007;25(1):55-63.

[45] Nissen M, Marshall H, Richmond P, et al. A randomized phase I study of the safety and immunogenicity of three ascending dose levels of a 3-antigen *Staphylococcus aureus* vaccine (SA3Ag) in healthy adults. Vaccine 2015;33(15):1846-54.

[46] Baker CJ, Paoletti LC, Wessels MR, et al. Safety and immunogenicity of capsular polysaccharide-tetanus toxoid conjugate vaccines for group B streptococcal types Ia and Ib. J Infect Dis 1999;179(1):142-50.

[47] Chen VL, Avci FY, Kasper DL. A maternal vaccine against group B *Streptococcus*: past, present, and future. Vaccine 2013;31(Suppl 4):D13-9.

[48] Cutland CL, Cunnington M, Olugbosi M, et al. Lessons learnt from enrolment and follow up of pregnant women and their infants in clinical trials in South Africa, a low-middle income country. Vaccine 2015;33(47):6406-12.

[49] Gruber WC, Scott DA, Emini EA. Development and clinical evaluation of Prevnar 13, a 13-valent pneumococcal CRM197 conjugate vaccine. Ann N Y Acad Sci. 2012;1263(1):15-26.

[50] Edwards MS, Lane HJ, Hillier SL, et al. Persistence of functional antibodies to group B streptococcal capsular polysaccharides following immunization with glycoconjugate vaccines. Vaccine 2012;30(28):4123-6.

[51] Madhi SA, Cutland CL, Jose L, et al. Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial. Lancet Infect Dis 2016;16(8):923-34.

[52] Heyderman RS, Madhi SA, French N, et al. Group B streptococcus vaccination in pregnant women with or without HIV in Africa: a nonrandomized phase 2, open-label, multicentre trial. Lancet Infect Dis 2016;16(5):546-55.

[53] Fluarix [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2018.

[54] Afluria [package insert]. Summit, NJ: Seqirus; 2018.

[55] Afluria Quadrivalent [package insert]. Summit, NJ: Seqirus; 2018.

[56] Morgan JL, Baggari SR, McIntire DD, et al. Pregnancy outcomes after antepartum tetanus, diphtheria, and acellular pertussis vaccination. Obstet Gynecol 2015;125(6):1433-8.

[57] Leroux-Roels G, Bebia Z, Maes C, et al. Safety and immunogenicity of a second dose of an investigational maternal trivalent group B streptococcus vaccine in nonpregnant women 4-6 years after a first dose: results from a phase 2 trial. Clin Infect Dis 2019;Aug 8 (epub ahead of print).

[58] Paoletti LC, Rench MA, Kasper DL, et al. Effects of alum adjuvant or a booster dose on immunogenicity during clinical trials of group B streptococcal type III conjugate vaccines. Infect Immun 2001;69(11):6696-701.

[59] US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

Document Approval Record

Document Name:	C1091007 Clinical Protocol, 07_Nov_2019
Document Title:	A PHASE 2, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY, TOL ERABILITY, AND IMMUNOGENICITY OF A BOOSTER DOSE OF A GROUP B STREPTOCOCCUS 6 VALENT POLYSACCHARIDE CON JUGATE VACCINE (GBS6) IN HEALTHY ADULTS

Signed By:	Date(GMT)	Signing Capacity
PPD	07-Nov-2019 17:31:18	Final Approval
PPD	08-Nov-2019 14:16:36	Final Approval