A PHASE 1/2, RANDOMIZED, PLACEBO-CONTROLLED, OBSERVER-BLINDED TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MULTIVALENT GROUP B STREPTOCOCCUS VACCINE IN HEALTHY NONPREGNANT WOMEN AND PREGNANT WOMEN 18 TO 40 YEARS OF AGE AND THEIR INFANTS

Study Intervention Number:	PF-06760805
Study Intervention Name:	Group B Streptococcus 6-Valent Polysaccharide Conjugate Vaccine (GBS6)
US IND Number:	17058
EudraCT Number:	2020-005074-96
ClinicalTrials.gov ID:	NCT03765073
Protocol Number:	C1091002
Phase:	1/2

Document History

Document	Version Date
Amendment 8	27 March 2023
Amendment 7	20 October 2022
Amendment 6	26 April 2022
Amendment 5	03 November 2021
Amendment 4	25 November 2020
Amendment 3	27 May 2020
Amendment 2	18 September 2019
Amendment 1	04 February 2019
Original Protocol	11 May 2018

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

Protocol Amendment Summary of Changes Table

Amendment 8 (27 March 2023)

Overall Rationale for the Amendment: The total number of participants enrolled from the United States (US) in Stage 3 is 54. The total number of participants enrolled from the US was initially 36 in protocol amendment 7. The number enrolled from the US is greater than 10% and is considered a substantial change. Furthermore, because of the additional enrolled participants from the US in protocol amendment 7, the duration of the study has increased from approximately 48 months to approximately 60 months.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1: Background and Rationale Section 2.2.5: Study Rationale Section 4.1: Diversity of Study Population Section 4.4: Stage 3 Section 4.7: Number of Participants Section 4.7.3: Stage 3 Section 10.1: Sample Size Determination Table 1. Enrollment and Dose Escalation Design	• Revised the number of enrolled participants in Stage 3 to the correct number enrolled (162 from South Africa/United Kingdom [UK] and 54 from the US)	• The number of enrolled participants from the US is greater than 10% indicated in protocol amendment 7.	• Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Table 2. Planned Participants: Total and Number in Each Stage and Group			
Section 4.6: Duration of the Study	• Updated the duration of the study	• Because of the addition of enrolled participants from the US in protocol amendment 7, the length of the study has increased.	• Substantial

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. PROTOCOL SUMMARY

1.1. Background and Rationale

Streptococcus agalactiae, also known as group B streptococcus (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 capsules. Although all GBS serotypes have been found to cause disease, 6 serotypes (Ia, Ib, II, III, IV, and V) have been found to cause over 85% of disease globally and 98% in South Africa, but there is variability in their global prevalence and virulence. GBS disease is most frequently found in the very young—newborns and infants younger than 3 months of age—and the elderly, especially older adults with comorbid conditions. However, disease due to GBS has been reported in individuals of all ages, and pregnant women may be particularly susceptible to GBS disease as well.

Among young infants, GBS is a leading cause of invasive bacterial infection, a significant cause of infant morbidity and mortality globally, and the leading infectious cause of morbidity and mortality in infants in the US. Serious GBS disease, including sepsis, meningitis, and pneumonia, is associated with mortality rates of 6% to 14% in high-income countries and 10% to 60% in low- and middle-income countries (LMICs). Of infants surviving GBS meningitis, one study found mild to moderate neurological sequelae in 25%, and 19% suffered severe sequelae, including cognitive delay, cerebral palsy, blindness, or hearing loss. Five serotypes (Ia, Ib, II, III, and V) are most frequently associated with GBS disease in infants. Another serotype (IV) shows a trend of increased prevalence in certain regions. GBS disease in infants is often classified as early-onset disease (EOD), which occurs within the first week of life, and late-onset disease (LOD), which occurs between Days 7 and 90.

The reported burden of infant GBS disease varies globally and is influenced by the intensity of the epidemiology surveillance for the organism, as well as by the frequency of healthcare interaction. This may therefore lead to the potential for underreporting, and underuse of intrapartum antibiotic prophylaxis (IAP) to prevent GBS disease. In regions, such as the US, where there are significant efforts and resources allocated for universal GBS screening of pregnant women and use of IAP to prevent GBS disease, it is notable that the number of cases of EOD decreased from a high of 1.7 cases/1000 live births since the early 1990s when recommendations for prevention were introduced to 0.21 cases/1000 live births in 2014. Despite declines in pediatric bacterial meningitis cases in the US between 2003 and 2007, the incidence in children <2 months of age was unchanged. This reflects the persistence of GBS LOD, which is the primary cause of bacterial meningitis in that age group. The incidence was 0.32 cases/1000 live births in 2015.

Vaccination of pregnant women has been 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. Vaccination with tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women was introduced in the US and in the UK in response to a significant upsurge in pertussis cases in all age groups.

Maternal immunization against influenza was recommended by the US Advisory Committee on Immunization Practices (ACIP) because of the increased risks of influenza and related complications in pregnant women. Safety surveillance conducted through 2012 has demonstrated no unusual patterns of pregnancy complications or fetal outcomes. Several countries recommend the administration of Tdap during every pregnancy, including closely spaced pregnancies. The South African guidelines for maternity care recommend all pregnant women are given 3 tetanus toxoid immunization doses during the first pregnancy and 2 tetanus toxoid immunization booster doses for the next 2 subsequent pregnancies, 1 in each pregnancy, at least 1 year apart.

Pfizer is developing a 6-valent capsular polysaccharide (CPS) conjugate vaccine (group B streptococcus 6-valent polysaccharide conjugate vaccine [GBS6]) aimed at the prevention of group B streptococcal disease due to 6 serotypes in young infants by active immunization of pregnant women. GBS6 has been developed based on Pfizer historical experience with licensed and investigational polysaccharide conjugate vaccines and published/public data with other investigational GBS CPS conjugate vaccines that have been evaluated in clinical trials, including a trivalent (Ia, Ib, and III) GBS CPS–cross-reactive material 197 (CRM_{197}) conjugate vaccine in pregnant women. Preclinical data show that GBS6 induces serotype-specific immunoglobulin G (IgG) responses and opsonophagocytic activity (OPA) that are protective against an infectious challenge in the offspring in animal models.

This Phase 1/2, randomized, placebo-controlled, observer-blinded study will be the first evaluation of the investigational GBS6 in pregnant women. This study will be conducted in 3 stages. Stage 1 will evaluate the safety, tolerability, and immunogenicity of GBS6 (20 µg CPS/serotype/dose) with and without aluminum phosphate ($AlPO_4$). This dose level was selected by the internal review committee (IRC) after the review of the unblinded safety data through 1 month after vaccination in an ongoing first-in-human (FIH), Phase 1/2, randomized, placebo-controlled, observer-blinded study that evaluated 3 ascending dose levels (5, 10, or 20 µg CPS/serotype/dose) of GBS6 formulated with or without $AlPO_4$ in healthy adults (nonpregnant women and men, 18 to 49 years of age) in the US (C1091001). Stage 2 will commence following a review of the 1-month postvaccination safety data from the Phase 1/2 LMIC Stage 1 cohort and 1-month postvaccination safety and immunogenicity data from the Phase 1/2 FIH study (C1091001). If the safety and immunogenicity profile is deemed acceptable, the safety, tolerability, and immunogenicity of 3 ascending dose levels (CCI [redacted] µg CPS/serotype/dose) of GBS6 formulated with or without $AlPO_4$ will be assessed when administered as a single dose to healthy pregnant women 18 to 40 years of age during their 27 to 36 weeks of pregnancy. Stage 2 will use a sentinel-cohort design with cohort progression (including progression into expanded cohorts) and dose escalation taking place after a safety review. In Stage 3, an additional cohort of healthy pregnant women will be enrolled to receive the selected GBS6 dose/formulation to provide an expanded safety and immunogenicity data set (both pregnant women and their infants) and to support progression of the development of this vaccine.

In Amendment 3, the gestational age of vaccination for participants in Stage 3 is expanding (from ≥27 0/7 to ≤35 6/7 weeks' gestation to ≥24 0/7 to ≤35 6/7 weeks' gestation) to enable expanded evaluation of safety and immunogenicity data at the selected dose, in the second and third trimesters of pregnancy.

In Amendment 4, Stage 1 participants (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 approximately 2 years after the primary dose of investigational product, to evaluate safety and immunogenicity following a booster dose of GBS6 in South African women. It is not known if GBS6 will be required during each pregnancy, thus information on the safety and immune response following a booster dose in different populations is important. Additionally, Stage 1 participants (nonpregnant women) will provide a large volume blood draw to support the development of a universal GBS vaccine reference standard assay.

In Amendment 5, Stage 1 booster participants (nonpregnant women) will return for an additional blood draw at Visit 10, which will take place approximately 14 to 184 days after Visit 9. This additional serum will further support the development of a universal GBS vaccine reference standard assay.

In Amendment 6, an additional 200 maternal participants will be added to Stage 3. These participants will be recruited at sites in the US. The data from these participants will contribute to the safety database to support the initiation of the Phase 3 program. These data will also enable an evaluation and comparison of GBS6 immune responses and placental antibody transfer efficiency between maternal/infant pairs in the US and South Africa. Furthermore, OPA analysis has been removed as an exploratory endpoint for Stage 1, Stage 2, and Stage 3 maternal and infant participants. It has also been removed as a secondary endpoint for Stage 1 participants. This is being removed because data from the second and third interim analyses demonstrated robust immune responses, as measured by serotype-specific IgG and functional antibody response for serotype-specific OPA after GBS6 vaccination. These data support the use of anti-GBS capsular IgG levels to evaluate GBS6 vaccine protection against invasive GBS disease. However, the lower limits of quantitation (LLOQs) for serotype-specific OPAs were high, indicating that the OPA assays are not sensitive enough compared to IgG, and thus rendering the OPA assay unsuitable for measuring vaccine protection.

In Amendment 7, there will be a revision of the infant blood draw schedule to remove blood draws at the 18-week postdelivery and 12-month postdelivery visits for infants born to maternal participants enrolled in the US and the UK Stage 3 cohort. The infant blood draws at these 2 visits are for the exploratory immunogenicity objective to describe immune responses to diphtheria and 13-valent pneumococcal conjugate vaccine administered to infant participants delivered to maternal participants vaccinated with GBS6, and are aligned with the South African pediatric immunization schedule. The pediatric immunization schedules in the US and the UK differ and are not aligned with the 18-week postdelivery and 12-month postdelivery study visits. This exploratory analysis will continue to be conducted in Stage 2 and Stage 3 infants born to maternal participants enrolled from South Africa as originally planned.

The adjusted proposed number of US participants, reduced from 200 to 36, will be sufficient to evaluate and compare the GBS6 placental antibody transfer efficiency between maternal/infant pairs in the US and South Africa. The amendment to exclusion criteria 8 and 15 for the Stage 3 maternal participants is clarification text to provide guidance to investigational sites, with respect to compliance with study protocol requirement, and will facilitate recruitment of suitable maternal participants for the study.

In Amendment 8, the total number of participants enrolled from the US in Stage 3 will be revised to the correct number enrolled (162 from South Africa/UK and 54 from the US). Furthermore, because of the additional enrolled participants from the US in protocol amendment 7, the duration of the study has increased from approximately 48 months to approximately 60 months.

Primary Objectives: Stage 1

- To describe the safety and tolerability of various GBS6 formulations in healthy nonpregnant women 18 to 40 years of age.
- To describe the safety and tolerability of a booster dose of GBS6 when administered to healthy nonpregnant women.

Primary Objectives: Stage 2

- To describe the safety and tolerability of various GBS6 formulations when administered to healthy pregnant women 18 to 40 years of age vaccinated at 27 to 36 weeks' gestation.
- To assess the safety of maternal immunization in infants born to women who were vaccinated with various GBS6 formulations during pregnancy.

Primary Objectives: Stage 3

- To describe the safety and tolerability of 1 selected dose/formulation of GBS6 when administered to healthy pregnant women 18 to 40 years of age vaccinated at 24 to 36 weeks' gestation.
- To assess the safety of maternal immunization in infants born to women 18 to 40 years of age who were vaccinated with 1 selected dose/formulation during pregnancy.

Primary Endpoints

Primary Endpoints: Stage 1

- Proportions of nonpregnant women reporting prompted local reactions within 7 days following administration of the primary and booster doses of investigational product (pain at the injection site, redness, and swelling).

- Proportions of nonpregnant women reporting prompted systemic events within 7 days following administration of the primary and booster doses of investigational product (fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain).

- Proportions of nonpregnant women reporting adverse events (AEs) through 1 month following administration of the primary and booster doses of investigational product.

- Proportions of nonpregnant women reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) through 6 months following administration of the primary dose and approximately 7 to 12 months following the booster dose of investigational product.

Primary Safety Endpoints (Maternal Participants): Stages 2 and 3

- Proportions of sentinel-cohort maternal participants (Stage 2 only) with clinical laboratory abnormalities following administration of investigational product at the 2-week follow-up visit.

- Proportions of maternal participants reporting prompted local reactions within 7 days following administration of investigational product (pain at the injection site, redness, and swelling).

- Proportions of maternal participants reporting prompted systemic events within 7 days following administration of investigational product (fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain).

- Proportions of maternal participants reporting AEs through 1 month after administration of investigational product.

- Proportions of maternal participants with SAEs, MAEs, and obstetric complications (prepartum, intrapartum, and postpartum) throughout the study (Visit 1 through the 12-month postdelivery study visit).

- Proportions of maternal participants with each delivery outcome (live birth, delivery mode).

Primary Safety Endpoints (Infant Participants): Stages 2 and 3

- Proportions of infant participants with specific birth outcomes.

- Proportions of infant participants with AEs from birth to 6 weeks of age.

- Proportions of infant participants with SAEs, AEs of special interest (major congenital anomalies, developmental delay, and suspected or confirmed GBS infection), and MAEs through 12 months of age.

Study Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of a multivalent GBS vaccine in healthy nonpregnant women and pregnant women 18 to 40 years of age and their infants. A total of approximately 622 participants (66 nonpregnant women and 556 maternal participants and their infants) will be enrolled in this study.

Stage 1

Nonpregnant women in good health will be screened, enrolled, and randomized in a 1:1:1 ratio (approximately 22 participants enrolled/group) to receive placebo (saline control) or GBS6 (20 µg CPS/serotype/dose) with or without $AlPO_4$. Participants will have blood drawn prior to vaccination (Visit 1), 2 weeks after vaccination (Visit 2), and 1 month after vaccination (Visit 3). Electronic diaries (e-diaries) will be used to collect prompted local reaction and systemic event data for 7 days after vaccination. AEs will be collected through 1 month after vaccination (Visit 3). In addition, MAEs and SAEs will be collected from screening through 6 months after vaccination (Visit 4).

A Pfizer IRC and an external data monitoring committee (EDMC) will review the 1-month postvaccination safety data (unblinded) from Stage 1 and the 1-month safety and immunogenicity data of the various GBS6 formulations from the FIH Phase 1/2 study before progression into Stage 2.

If a dose level or formulation does not demonstrate the expected 1-month immunogenicity in the FIH Phase 1/2 study (C1091001) or acceptable safety profile in Stage 1 of this Phase 1/2 study, that dose level or formulation will not be evaluated in Stage 2.

The study will proceed to Stage 2 at the discretion of the IRC in consultation with the EDMC.

Stage 1 participants (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 approximately 2 years after the primary dose of investigational product. Participants will have blood drawn at the prebooster screening visit (Visit 5), prior to the booster vaccination (Visit 6), 1 month after the booster vaccination (Visit 7), 3 months after the booster vaccination (Visit 8), 6 months after the booster vaccination (Visit 9), and at the blood draw follow-up visit after the booster vaccination (Visit 10). E-diaries will be used to collect prompted local reaction and systemic event data for 7 days after the booster vaccination. AEs will be collected through 1 month after vaccination (Visit 7). In addition, MAEs and SAEs will be collected from the booster vaccination visit (Visit 6) through approximately 7 to 12 months after the booster vaccination (Visit 10).

Stage 2

Approximately 360 pregnant women (once consented will be referred to as "maternal participants") will be screened for general health, health of the pregnancy, and gestational age. Stage 2 will utilize a sentinel-cohort design, with cohort progression and dose escalation taking place after a safety review (data from each maternal participant through 14 days after vaccination) of the sentinel cohort of participants at each dose level. The first 42 eligible maternal participants at each dose level will be referred to as the sentinel cohort. Starting with the lowest dose level, maternal participants will be randomly assigned (in a 1:1:1 ratio, 14 participants per group) to receive a single dose of GBS6, formulated with or without $AlPO_4$, or placebo (saline control) within the sentinel cohort of a given dose level. The enrollment rate in the sentinel cohort will be limited to a maximum of 5 participants per day. A review of the 14-day safety data in a sentinel cohort will be conducted by the Pfizer IRC, and if deemed acceptable, will trigger:

- enrollment in the expanded cohort at that dose level (1:1:1 ratio, 26 participants per group), with no prespecified limit on daily enrollment until approximately 78 additional maternal participants are enrolled, and

- enrollment in the sentinel cohort for the next higher dose level.

Enrollment will proceed this way in a staggered fashion through the highest dose level.

This study will use stopping rules for the sentinel cohort, and 1 stopping rule (serious, unexpected AE considered possibly related to vaccine) will also apply to the expanded-cohort enrollment phase. Stopping rules (and the decision to terminate or restart at a given dose level) may be applied independently for each formulation at the discretion of the Pfizer IRC in conjunction with the EDMC. It is possible that after a stopping rule is met at a given dose level, one formulation (with or without $AlPO_4$) may proceed while the other may not.

The IRC will meet after each interim analysis to review safety and immunogenicity data, and on an ad hoc and timely basis to review safety data if a stopping rule is triggered, and to make recommendations for the study. In addition, the EDMC will meet for regular review of accumulating safety data and for ad hoc review if a stopping rule is met.

At Visit 1, e-diaries will be used to collect systemic event data at baseline as well as prompted local reaction and systemic event data for 7 days after vaccination. In maternal participants, the investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through Visit 3. At 1 week following delivery (Visit 5), the participant will be contacted by telephone to inquire about MAEs and SAEs, including hospitalizations, since Visit 3. At all subsequent visits (Visits 6, 7, 8, and 9), only MAEs and SAEs, including hospitalizations, will be reported. In addition, AEs occurring up to 48 hours after the Visit 4, Visit 6, and Visit 9 blood draws that are related to study procedures will also be reported.

For infant participants, the investigator and site staff will ensure the active elicitation and collection of AEs and SAEs from birth (Visit 1) through Visit 3. At subsequent visits (Visits 4, 5, 6, and 7), only AEs of special interest, MAEs, and SAEs, including hospitalizations, will be reported. In addition, AEs occurring up to 48 hours after the Visit 4, 5, and 7 blood draws and up to 48 hours after the Visit 4 CCI samples that are related to study procedures will be reported.

In maternal participants, blood samples for immunogenicity assessments will be taken at Day 1 (Visit 1), 2 weeks (Visit 2) and 1 month (Visit 3) after vaccination, at delivery (Visit 4) (blood may be collected from maternal participants up to 72 hours after delivery), and 6 weeks (Visit 6) and 12 months (Visit 9) after delivery.

In infant participants, cord blood will be collected at delivery (blood may be collected in the infant participants up to 72 hours after delivery if cord blood is unavailable) (Visit 1) and blood will be drawn at 6 and 14 weeks of age (Visits 3 and 4) for GBS6 antibody assessments. CCI

CCI

When all Stage 2 sentinel-cohort maternal participants and their infant participants have completed the delivery/birth visit, safety and immunogenicity data will be unblinded and reviewed, when available, by the IRC for Pfizer informational and planning purposes.

When all Stage 2 maternal participants and their infant participants have completed the delivery/birth visit, safety and immunogenicity data will be unblinded by group, when available, and analyzed and reviewed by the Pfizer IRC. The final GBS6 dose and formulation to take into Stage 3 and further development will be selected after this review.

Stage 3

Approximately 216 additional maternal participants will be enrolled in Stage 3 (approximately 162 from South Africa/UK and 54 from the US) to receive a single dose/formulation of the selected GBS6 or placebo (saline control) in a 1:1 ratio. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks. There will be no dose escalation, no sentinel cohorts, and no planned stopping rules. The visit schedule, follow-up, and assessments for maternal participants and their infant participants will be similar to Stage 2. The additional data from Stage 3 will contribute to the safety database of maternal participants to support the design the Phase 3 program.

When Stage 3 maternal participants and their infant participants have completed the delivery/birth visit, safety and immunogenicity data will be unblinded by group, when available, and analyzed and reviewed by the Pfizer IRC.

Investigational Products

The investigational products are GBS6, composed of CPS of serotypes Ia, Ib, II, III, IV, and V, individually conjugated to CRM_{197} at dose levels of [redacted] µg CPS/serotype/dose, formulated with or without $AlPO_4$, or placebo (saline control). At Visit 1, investigational product will be administered intramuscularly by [redacted], preferably of the nondominant arm.

Statistical Methods

Statistical analyses will be descriptive in nature. All safety and immunogenicity data will be analyzed separately for nonpregnant women (Stage 1), maternal participants (Stage 2 and Stage 3), and their infant participants (Stage 2 and Stage 3). Safety and immunogenicity data from maternal and infant participants in Stage 2 and Stage 3 will be analyzed separately.

Descriptive summary statistics will be provided for all data. For continuous outcomes, the summary statistics include number of participants, mean, standard deviation, median, minimum, and maximum, and 2-sided 95% confidence intervals (CIs) for the mean, as needed. For categorical outcomes, number and percentage of participants in each category and 2-sided 95% CI will be provided.

1.2. Schedule of Activities

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures (Section 7) and Assessments (Section 8) sections 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 on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Stage 1 – Schedule of Activities for Nonpregnant Women											
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-Up Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Telephone Contact**	**Prebooster Screening**	**Booster Vaccination**	**1-Month Booster Vaccination Follow-Up Visit**	**3-Month Booster Vaccination Follow-Up Visit**	**6-Month Booster Vaccination Follow-Up Visit**	**Blood Draw Follow-Up Visit**
Visit Window (Days)[a]	**Day -7 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**160-200 Days After Visit 1**	**Day -7 to Day -2 Prior to Visit 6**	**~2 Years After Visit 1**	**28-42 Days After Visit 6**	**84-126 Days After Visit 6**	**160-200 Days After Visit 6**	**14-184 Days After Visit 9**
Informed consent	X					X[b]					X[b]
Demography	X										
Medical history	X					X[c]					
Vital signs[d]	X	X				X					
Measure oral temperature							X				
Physical examination	X					X					
HIV, HBV, and HCV testing (~5-mL blood sample)	X					X					
Urine pregnancy test		X					X				
Record nonstudy vaccine information	X	X	X	X		X	X	X			
Record concomitant medication	X	X	X	X	X[e]	X	X	X	X[e]	X[e]	X[e]
Review inclusion and exclusion criteria	X					X					
Review screening laboratory results		X					X				

Stage 1 – Schedule of Activities for Nonpregnant Women											
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-Up Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Telephone Contact**	**Prebooster Screening**	**Booster Vaccination**	**1-Month Booster Vaccination Follow-Up Visit**	**3-Month Booster Vaccination Follow-Up Visit**	**6-Month Booster Vaccination Follow-Up Visit**	**Blood Draw Follow-Up Visit**
Visit Window (Days)[a]	**Day -7 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**160-200 Days After Visit 1**	**Day -7 to Day -2 Prior to Visit 6**	**~2 Years After Visit 1**	**28-42 Days After Visit 6**	**84-126 Days After Visit 6**	**160-200 Days After Visit 6**	**14-184 Days After Visit 9**
Contraception check[f]		X	X	X	X		X	X	X	X	X
Review temporary delay criteria		X					X				
Review continued eligibility		X	X	X		X	X	X	X	X	X
Assign single participant identifier	X										
Assign participant randomization and container number		X									
Assign container number							X				
Blood draw (~15 mL per blood sample) for immunogenicity assessment[CCI]		X	X	X			X	X	X	X	
CCI											
Large volume blood draw for development of a universal GBS vaccine reference standard assay						25 mL	125 mL	125 mL	125 mL	125 mL	125 mL
Administer investigational product		X					X				
Postvaccination observation (30 minutes) and assessment of immediate adverse events		X					X				
Dispense e-diary, thermometer, and measuring device[h]		X					X				

Stage 1 – Schedule of Activities for Nonpregnant Women											
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-Up Visit**	**1-Month Follow-Up Visit**	**6-Month Follow-Up Telephone Contact**	**Prebooster Screening**	**Booster Vaccination**	**1-Month Booster Vaccination Follow-Up Visit**	**3-Month Booster Vaccination Follow-Up Visit**	**6-Month Booster Vaccination Follow-Up Visit**	**Blood Draw Follow-Up Visit**
Visit Window (Days)[a]	**Day -7 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**160-200 Days After Visit 1**	**Day -7 to Day -2 Prior to Visit 6**	**~2 Years After Visit 1**	**28-42 Days After Visit 6**	**84-126 Days After Visit 6**	**160-200 Days After Visit 6**	**14-184 Days After Visit 9**
Review and/or collect e-diary[i]		X	X				X	X			
Record adverse events	X	X	X	X		X	X	X			
Record medically attended adverse events and serious adverse events	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]											

Abbreviations: e-diary = electronic diary; GBS = group B streptococcus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

a. Day relative to the start of study vaccination (Day 1).
b. Obtain written informed consent before performing any study-specific procedures.
c. Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures, that have been diagnosed since Visit 1.
d. Vital signs include weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
e. Only concomitant medication taken to treat an adverse event will be recorded in the case report form.
f. The contraception check is an opportunity to confirm that contraception was/is used consistently and correctly.

CCI [redacted]

h. Participants will record reactogenicity events in an e-diary within a fixed time window each day for 7 days following 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 7 following vaccination to determine if an unscheduled visit is required.
i. Designated site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

CCI [redacted]

Stages 2 and 3 – Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2[a]**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening[b]**	**Vaccination**	**2-Week Follow-Up Visit[b]**	**1-Month Follow-Up Visit**	**Delivery**	**1-Week Postdeliv. Follow-Up**	**6-Week Postdeliv. Follow-Up**	**14-Week Postdeliv. Follow-Up**	**6-Month Postdeliv. Follow-Up**	**12-Month Postdeliv. Follow-Up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**80-100 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Informed consent	X									
Demography	X									
Record current alcohol and tobacco usage	X									
Medical history including obstetric and gestational history	X									
Record LMP and EDD	X									
Vital signs[c]	X	X	X	X						
Physical examination	X									
Targeted physical examination		X	X	X			X			
Obstetric examination	X	X	X	X						
Obstetric ultrasound	X									
Record nonstudy vaccine information	X	X	X	X	X					
Record concomitant medication	X	X	X	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Record use of antibiotic medication	X	X	X	X	X	X	X	X	X	X
Review eligibility criteria	X									
Review screening laboratory results		X								
Review temporary delay criteria		X								
Review continued eligibility		X	X	X	X	X	X	X	X	X
Record systemic events at baseline in the e-diary		X								
Assign single participant identifier	X									

Stages 2 and 3 – Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2[a]**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening[b]**	**Vaccination**	**2-Week Follow-Up Visit[b]**	**1-Month Follow-Up Visit**	**Delivery**	**1-Week Postdeliv. Follow-Up**	**6-Week Postdeliv. Follow-Up**	**14-Week Postdeliv. Follow-Up**	**6-Month Postdeliv. Follow-Up**	**12-Month Postdeliv. Follow-Up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**80-100 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Assign participant randomization and container number		X								
Blood draw for immunogenicity assessment (~15 mL per blood sample)CCI		X	X	X	X[f]		X			X
CCI										
Administer investigational product		X								
Postvaccination observation (30 minutes) and assessment of immediate adverse events		X								
Dispense e-diary, thermometer, and measuring device[g]		X								
Review and/or collect e-diary[h]		X	X							
Record pregnancy outcome information					X					
Record adverse events	X	X	X	X	X[i]		X[i]			X[i]
Record medically attended adverse events and serious adverse events	X	X	X	X	X	X	X	X	X	X
CCI										
Blood draw for HBV, HCV, HIV, and syphilis testing (~10 mL)	X									

Stages 2 and 3 – Schedule of Activities for Maternal Participants										
Visit Number	**0**	**1**	**2[a]**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening[b]**	**Vaccination**	**2-Week Follow-Up Visit[b]**	**1-Month Follow-Up Visit**	**Delivery**	**1-Week Postdeliv. Follow-Up**	**6-Week Postdeliv. Follow-Up**	**14-Week Postdeliv. Follow-Up**	**6-Month Postdeliv. Follow-Up**	**12-Month Postdeliv. Follow-Up**
Visit Window (Days)	**Day -14 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**Varies**	**7-10 Days After Visit 4**	**35-49 Days After Visit 4**	**80-100 Days After Visit 4**	**160-200 Days After Visit 4**	**365-385 Days After Visit 4**
Type of Visit	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Blood draw (~10 mL) for hematology and chemistry assessments (**Stage 2 sentinel cohort only**)[e]	X		X							
Urine sample for glucose and protein testing	X	X								

Abbreviations: EDD = estimated date of delivery; e-diary = electronic diary; GBS = group B streptococcus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LMP = last menstrual period; Postdeliv. = postdelivery; Vacc. = vaccination.

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

a. Visits at 2 weeks and 1 month after vaccination will not be performed if delivery occurs before the visits. In that case, hematology, and chemistry assessments due at the 2-week visit should be conducted at the delivery visit. Once delivery occurs, the visit windows are calculated based on delivery date.
b. If abnormal laboratory values (as defined in Screening, Section 7.2.1, and in Section 8.5.3) are reported at Visit 0/Visit 2 and the investigator believes the results to be erroneous, the abnormal laboratory parameters may be retested.
c. Vital signs include weight, height (only required at Visit 0), oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
d. Only concomitant medication taken to treat an adverse event will be recorded in the case report form.
CCI
f. Blood sample may be collected up to 72 hours after delivery.
g. Participants will provide (in an e-diary) a baseline assessment of prompted systemic events prior to vaccination and participants will record (in an e-diary) reactogenicity events within a fixed time window each day for 7 days following 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 7 following vaccination to determine if an unscheduled visit is required (see Section 7.4).
h. Designated site staff will review e diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.
i. Only adverse events occurring up to 48 hours after each blood draw that are related to study procedures must be recorded in the case report form.
CCI

Stages 2 and 3 – Schedule of Activities for Infant Participants							
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Equivalent Visit Number for Maternal Participants	**4**	**5**	**6**	**7**	**N/A**	**8**	**9**
Visit Description	**Delivery**	**1-Week Postdelivery Follow-Up**	**6-Week Postdelivery Follow-Up**	**14-Week Postdelivery Follow-Up**	**18-Week Postdelivery Follow-Up**	**6-Month Postdelivery Follow-Up**	**12-Month Postdelivery Follow-Up**
Visit Window (Days)	**Varies**	**7-10 Days After Visit 1**	**35-49 Days After Visit 1**	**80-100 Days After Visit 1**	**119-133 Days After Visit 1**	**160-200 Days After Visit 1**	**365-385 Days After Visit 1**
Type of Visit	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Assign single participant identifier	X						
Record demography and available birth information (including Ballard score)[a]	X						
Vital signs[b]	X		X	X	X		X
Physical examination	X		X	X	X		X
Record concomitant medication	X	X	X	X[c]	X[c]	X[c]	X[c]
Record use of antibiotic medication	X	X	X	X	X	X	X
Record nonstudy vaccine information	X	X	X	X	X	X	X
Review continued eligibility	X	X	X	X	X	X	X
Record breastfeeding information		X	X	X	X	X	X
Blood draw (~5 mL per blood sample)[d]			X	X	X		X
Blood draw US and UK Stage 3 participants (~5 mL per blood sample)[d]			X	X			
Cord blood sample[e] (~10 mL)[d] for immunogenicity assessment	X						

Stages 2 and 3 – Schedule of Activities for Infant Participants							
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Equivalent Visit Number for Maternal Participants	**4**	**5**	**6**	**7**	**N/A**	**8**	**9**
Visit Description	**Delivery**	**1-Week Postdelivery Follow-Up**	**6-Week Postdelivery Follow-Up**	**14-Week Postdelivery Follow-Up**	**18-Week Postdelivery Follow-Up**	**6-Month Postdelivery Follow-Up**	**12-Month Postdelivery Follow-Up**
Visit Window (Days)	**Varies**	**7-10 Days After Visit 1**	**35-49 Days After Visit 1**	**80-100 Days After Visit 1**	**119-133 Days After Visit 1**	**160-200 Days After Visit 1**	**365-385 Days After Visit 1**
Type of Visit	**Hospital**	**Phone Call**	**Clinic**	**Clinic**	**Clinic**	**Phone Call**	**Clinic**
Blood spot card collection[f]	X						
Record adverse events	X	X	X	X[g]	X[g]		X[g]
CCI							
Record medically attended adverse events, serious adverse events, and adverse events of special interest	X	X	X	X	X	X	X

Abbreviations: GBS = group B streptococcus; N/A = not applicable.

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

a. If the Ballard score is unavailable, it may be calculated and recorded up to 72 hours after delivery.
b. Vital signs include weight, height (length at Visit 1), head circumference, axillary temperature, pulse rate, and respiratory rate.
c. Only concomitant medication taken to treat an adverse event will be recorded in the case report form.
d. All blood volumes are approximate.
e. If cord blood is unavailable, then a 2.5-mL blood sample may be collected in the infant participants up to 72 hours after delivery.
f. Blood spot card collection will be performed using cord blood sample, or blood draw (up to 72 hours after delivery) if cord blood unavailable.
g. Only adverse events occurring up to 48 hours after each blood draw/swab collection that are related to study procedures must be recorded in the case report form.

CCI

2. INTRODUCTION

2.1. Indication

Group B streptococcus 6-valent polysaccharide conjugate vaccine (GBS6) is being developed for:

- Active immunization to prevent disease caused by group B streptococcus (GBS) serotypes contained in the vaccine.

2.2. Background and Rationale

2.2.1. Disease Overview

Streptococcus agalactiae, also known as GBS, is an encapsulated, gram-positive coccus that is associated with lower intestinal and rectovaginal colonization. There are 10 serotypes of GBS (Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX) differentiated by the polysaccharide composition of their capsules. Although all GBS serotypes have been found to cause disease, 6 serotypes (Ia, Ib, II, III, IV, and V) have been found to cause over 85% of disease globally and 98% in South Africa,[1] but there is variability in their global prevalence and virulence.[2,3] GBS disease is most frequently found in the very young—newborns and infants younger than 3 months of age—and the elderly, especially older adults with comorbid conditions.[4,5,6] However, disease due to GBS has been reported in individuals of all ages, and pregnant women may be particularly susceptible to GBS disease as well.[7] Among infants, GBS may cause serious disease, including sepsis, meningitis, and pneumonia; less common manifestations include skin and soft tissue, bone, and joint infections.[8] 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).[9] Bacteremia without a focus, cellulitis, bone and joint infections, and urinary tract infections are common disease manifestation of GBS infection in older nonpregnant adults.[5,10,11]

2.2.2. GBS Disease in Infants and Pregnant Women

GBS is a leading cause of invasive bacterial infection in young infants and a significant cause of infant morbidity and mortality globally.[5,12,13] The US Centers for Disease Control and Prevention (CDC) notes that it is a leading infectious cause of morbidity and mortality in infants in the US.[14] Serious GBS disease, including sepsis, meningitis, and pneumonia, is associated with mortality rates of 6% to 14% in high-income countries and 10% to 60% in low- and middle-income countries (LMICs).[13,15,16,17] Of infants surviving GBS meningitis, one study found mild to moderate neurological sequelae in 25%, and 19% suffered severe sequelae, including cognitive delay, cerebral palsy, blindness, or hearing loss.[18] Five serotypes (Ia, Ib, II, III, and V) are most frequently associated with GBS disease in infants. Another serotype (IV) shows a trend of increased prevalence in certain regions.[5] GBS disease in infants is often classified as early-onset disease (EOD), which occurs within the first week of life, and late-onset disease (LOD), which occurs between Days 7 and 90.[6] The most common clinical syndrome in EOD is sepsis/bacteremia without a focus, whereas LOD is more likely to be associated with a focus,[4,6,15] with meningitis being more common in LOD (21%-59% of LOD cases).[4,6,15]

Additionally, serotype III appears to be a relatively prominent cause of LOD (causing 51%-67% of LOD),[4,6,15] whereas there appears to be greater diversity of serotypes causing EOD.

The reported burden of infant GBS disease varies globally and is influenced by the intensity of the epidemiology surveillance for the organism, as well as by the frequency of healthcare interaction. This may therefore lead to the potential for underreporting, and underuse of intrapartum antibiotic prophylaxis (IAP) to prevent GBS disease.[1] In regions, such as the US, where there are significant efforts and resources allocated for universal GBS screening of pregnant women and use of IAP to prevent GBS disease, it is notable that the number of cases of EOD decreased from a high of 1.7 cases/1000 live births since the early 1990s when recommendations for prevention were introduced to 0.21 cases/1000 live births in 2014.[19,20] Despite declines in pediatric bacterial meningitis cases in the US between 2003 and 2007, the incidence in children <2 months of age was unchanged. This reflects the persistence of GBS LOD, which is the primary cause of bacterial meningitis in that age group.[21] The incidence was 0.32 cases/1000 live births in 2015.[20]

Some of the highest rates of GBS disease and highest case fatality rates are found in infant populations in Africa.[1,12] Surveillance conducted in South Africa in 3 secondary/tertiary hospitals in Johannesburg from November 2012 to February 2014 found the rate of infant invasive GBS disease to be 2.38 cases/1000 births.[15] Human immunodeficiency virus (HIV)-exposed infants had a higher rate compared to unexposed infants. The overall case fatality rate of GBS disease was 18%, and most deaths occurred within 48 hours of hospitalization or birth. Meningitis was part of the clinical syndrome in 30% of surviving infants. Follow-up screening in the study found neurological abnormalities at 3 months of age in 13% of the infants who recovered from GBS disease.[15] GBS has also been implicated as a cause of stillbirth in countries with few resources (up to approximately 12% suggested in one review); evaluation of GBS as a contributing factor in stillbirth is an active area of research.[22] The rates of GBS disease in other African nations have been estimated at 1.3/1000 live births (Gambia in 2016)[23] and 1.8/1000 live births (Malawi in 2007).[24] Because of the burden of disease and its potentially devastating sequelae, GBS infection remains an important public health target.

GBS disease in pregnant and postpartum women does not appear to have been reduced through the introduction of IAP in the US,[14] as may be expected given the short course of administration during the intrapartum period only. In South Africa, IAP practices vary across the country and cases of neonatal sepsis are generally managed at secondary hospitals in each province. IAP is not based on screening of pregnant women to identify rectovaginal colonization at 35 to 37 weeks of gestational age (GA), and formal guidelines using a clinical risk-based approach are implemented in some institutions (eg, Chris Hani Baragwanath Hospital in Soweto), but not at other institutions. The impact of IAP on GBS disease in South Africa is therefore difficult to assess.[25]

In other countries, such as in certain European countries, where interventions are less widely used or a risk-based approach is used, the trend in incidence rates may be unchanged or increasing slightly.[6,26] Neither approach has eliminated GBS disease in infants.

Furthermore, many countries around the world do not have the resources to implement IAP. Even with potential underreporting, the highest rates of GBS disease are found in LMICs,[15] where healthcare access and standards of prenatal care may vary, or the resources for significant preventive interventions are not available.

2.2.3. Rationale for Development of GBS6

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

Vaccination of pregnant women has been 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.[27,28] Tetanus toxoid vaccine has been used to vaccinate pregnant women in parts of the world for many years as an effective tool to induce immunoglobulin G (IgG) antibodies that cross the placenta and after birth prevent neonatal tetanus.[28] There is also increasing experience on the safety, effectiveness, and acceptance of influenza vaccine and tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap) for use in pregnant women in various regions of the world to prevent disease in newborns and infants. Maternal immunization against influenza was recommended by the US Advisory Committee on Immunization Practices (ACIP) in 2004.[29] In addition, in 2009, because of the increased risks of influenza and related complications in pregnant women, the ACIP recommended that pregnant women receive both the inactivated influenza A H1N1 (2009) monovalent vaccine and the inactivated seasonal influenza vaccine during any stage of pregnancy.[30] Safety surveillance conducted through 2012 has demonstrated no unusual patterns of pregnancy complications or fetal outcomes.[31] In the US, Tdap vaccination was initially introduced for unvaccinated pregnant women, and further expanded to all pregnancies in 2012. The UK also introduced a Tdap vaccination program of pregnant women; both of these measures were taken in response to a significant upsurge in pertussis cases in all ages. To date (2013), these vaccines have demonstrated an acceptable safety profile with single and repeat dosing.[32,33]

2.2.3.2. 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.[34] The efficiency of antibody transfer depends on placental integrity, maternal total IgG, GA at delivery, and IgG subclass (the [CCI] subclass is most efficiently transferred).[28] 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. There 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.[35] Since the initial study, additional work was conducted demonstrating the correlation between serotype Ia–specific anti–capsular polysaccharide (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.[36-39] 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.

2.2.3.3. Clinical Experience With Polysaccharide Conjugate Vaccines 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.[40,41] A number of polysaccharide conjugate vaccines have been developed and globally licensed by Pfizer (HibTITER®, Meningitec®, Prevenar®, Prevenar 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.

Investigational GBS polysaccharide conjugate vaccines have been evaluated in clinical trials in pregnant women, including a trivalent (Ia, Ib, and III) GBS CPS–cross-reactive material 197 (CRM_{197}) conjugate vaccine in South Africa.[42,43] 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.

2.2.3.4. 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 the administration of Tdap during every pregnancy, including closely spaced pregnancies. The South African guidelines for maternity care recommend all pregnant women are given a total of 5 properly spaced doses of tetanus toxoid immunization to provide life-long protection against tetanus.
The guidelines recommend 3 tetanus toxoid immunization doses during the first pregnancy and 2 tetanus toxoid immunization booster doses for the next 2 subsequent pregnancies, 1 in each pregnancy, at least 1 year apart.[44] Published data report that vaccination with Tdap during pregnancy is not associated with an increased risk of adverse birth outcomes[45] and suggest that repetitive dosing in a short time span in serial pregnancies does not unfavorably affect pregnancy. In 1 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.[46]

Data are available regarding the boosting of IgG responses from Phase 1 and 2 clinical trials of other GBS candidate vaccines. In 1 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.[47]

In another study investigating a different GBS candidate vaccine, a second dose of GBS type III CPS-tetanus toxoid conjugate vaccine (GBS III-TT) 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.[48] These data suggest that repeat vaccination is safe and may offer immunologic benefit.

2.2.4. Group B Streptococcus 6-Valent Polysaccharide Conjugate Vaccine

Pfizer is developing a GBS6 vaccine aimed at the prevention of GBS disease due to 6 serotypes in young infants by active immunization of pregnant women.

The GBS6 candidates are composed of polysaccharides of the 6 most prevalent serotypes causing >95% of GBS disease in infants, individually conjugated to the CRM_{197} carrier protein. They contain CCI µg CPS/serotype/dose, and are formulated with or without aluminum phosphate ($AlPO_4$). Refer to Table 3 for further details. The candidates have been developed based on Pfizer historical 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.[41,49-57]

The CPS/serotype/dose is within the range clinically evaluated in monovalent and multivalent vaccines of GBS polysaccharide conjugated to tetanus toxoid or CRM_{197}.[50,58,59] These investigational vaccines have also been evaluated in pregnant women in clinical studies, with no safety concerns identified to date. Preclinical data show that GBS6 induces serotype-specific IgG responses and opsonophagocytic activity (OPA) that are protective against an infectious challenge in the offspring in animal models.

The formulations with $AlPO_4$ may offer particular advantages in immune response based on their potential to drive an CCI antibody response, which is the antibody subclass preferentially transported across the placenta.[60,61] Therefore, GBS6 formulated with $AlPO_4$ is being assessed in early clinical development to determine the optimal formulation that induces maximally protective antibody levels in humans.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the GBS6 investigator's brochure (IB).

2.2.5. Study Rationale

This Phase 1/2, randomized, placebo-controlled, observer-blinded study will be the first evaluation of the investigational GBS6 in pregnant women. This study will be conducted in 3 stages.

Stage 1 will evaluate the safety, tolerability, and immunogenicity of GBS6 (20 µg CPS/serotype/dose) with and without $AlPO_4$. This dose level was selected by the internal review committee (IRC) after the review of the unblinded safety data through 1 month after vaccination in an ongoing first-in-human (FIH), Phase 1/2, randomized, placebo-controlled, observer-blinded study that evaluated 3 ascending dose levels (5, 10, or 20 µg CPS/serotype/dose) of GBS6 formulated with or without $AlPO_4$ in healthy adults (nonpregnant women and men, 18 to 49 years of age) in the US (Study C1091001).

Stage 2 will commence following a review of the 1-month postvaccination safety data from the Phase 1/2 LMIC Stage 1 cohort and 1-month postvaccination safety and immunogenicity data from the Phase 1/2 FIH study (C1091001). If the safety and immunogenicity profile is deemed acceptable, the safety, tolerability, and immunogenicity of 3 ascending dose levels (CCI [redacted] µg CPS/serotype/dose) of GBS6 formulated with or without $AlPO_4$ will be assessed when administered as a single dose to healthy pregnant women 18 to 40 years of age during their 27 to 36 weeks of pregnancy. Of note, all 3 dose levels (CCI [redacted] µg CPS/serotype/dose) may not be evaluated during Stage 2 should any dose/formulation level be deemed unacceptable after review of immunogenicity data from the Phase 1/2 FIH study (C1091001) and the safety data from Stage 1 of the C1091002 study.

Stage 2 will use sentinel cohorts to assess safety to allow progression to the next higher dose. These sentinel cohorts serve as a Phase 1 evaluation in the study based on the small number of participants in the cohort and the focus on safety, including safety laboratory assessments. Enrollment of the remaining cohorts serves as the Phase 2 component of the study and will provide an increased number of maternal participants for immunogenicity assessment as well as expand the safety data set. Safety and GBS6 antibody transfer to infants born from vaccinated women will be evaluated. A single dose and formulation for further evaluation in Stage 3 of the study will be selected after review of the delivery safety and immunogenicity data from maternal participants and their infant participants. In Stage 3, an additional cohort of healthy pregnant women will be enrolled to receive the selected GBS6 dose/formulation to provide an expanded safety and immunogenicity data set (both pregnant women and their infant participants) and to support progression of the development of this vaccine.

This study will describe the safety of GBS6 in pregnant women and their infant participants. It will also assess the immunogenicity of GBS6 in pregnant women, the transfer of anticapsular antibody to their infant participants, and the kinetics of antibody transfer in the infant participants. CCI [redacted]

In Amendment 3, the gestational age of vaccination for participants in Stage 3 is expanding (from ≥27 0/7 to ≤35 6/7 weeks' gestation to ≥24 0/7 to ≤35 6/7 weeks' gestation) to enable expanded evaluation of safety and immunogenicity data at the selected dose, in the second and third trimesters of pregnancy.

In Amendment 4, Stage 1 participants (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 approximately 2 years after the primary dose of investigational product, to evaluate safety and immunogenicity following a booster dose of GBS6 in South African women. It is not known if GBS6 will be required during each pregnancy, thus information on the safety and immune response following a booster dose in different populations is important. Additionally, Stage 1 participants (nonpregnant women) will provide a large volume blood draw to support the development of a universal GBS vaccine reference standard assay.

In Amendment 5, Stage 1 booster participants (nonpregnant women) will return for an additional blood draw at Visit 10, which will take place approximately 14 to 184 days after Visit 9. This additional serum will further support the development of a universal GBS vaccine reference standard assay.

In Amendment 6, an additional 200 maternal participants will be added to Stage 3. These participants will be recruited at sites in the US. The data from these participants will contribute to the safety database to support the initiation of the Phase 3 program. These data will also enable an evaluation and comparison of GBS6 immune responses and placental antibody transfer efficiency between maternal/infant pairs in the US and South Africa. Furthermore, OPA analysis has been removed as an exploratory endpoint for Stage 1, Stage 2, and Stage 3 maternal and infant participants. It has also been removed as a secondary endpoint for Stage 1 participants. This is being removed because data from the second and third interim analyses demonstrated robust immune responses, as measured by serotype-specific IgG and functional antibody response for serotype-specific OPA after GBS6 vaccination. These data support the use of anti-GBS capsular IgG levels to evaluate GBS6 vaccine protection against invasive GBS disease. However, the lower limits of quantitation (LLOQs) for serotype-specific OPAs were high, indicating that the OPA assays are not sensitive enough compared to IgG, and thus rendering the OPA assay unsuitable for measuring vaccine protection.

In Amendment 7, there will be a revision of the infant blood draw schedule to remove blood draws at the 18-week postdelivery and 12-month postdelivery visits for infants born to maternal participants enrolled in the US and the UK Stage 3 cohort. The infant blood draws at these 2 visits are for the exploratory immunogenicity objective to describe immune responses to diphtheria and 13-valent pneumococcal conjugate vaccine administered to infant participants delivered to maternal participants vaccinated with GBS6, and are aligned with the South African pediatric immunization schedule. The pediatric immunization schedules in the US and the UK differ and are not aligned with the 18-week postdelivery and 12-month postdelivery study visits. This exploratory analysis will continue to be conducted in Stage 2 and Stage 3 infants born to maternal participants enrolled from South Africa as originally planned.

The adjusted proposed number of US participants, reduced from 200 to 36, will be sufficient to evaluate and compare the GBS6 placental antibody transfer efficiency between maternal/infant pairs in the US and South Africa. The amendment to exclusion criteria 8 and 15 for the Stage 3 maternal participants is clarification text to provide guidance to investigational sites, with respect to compliance with study protocol requirement, and will facilitate recruitment of suitable maternal participants for the study.

Data from this study will be used to progress the development of this vaccine into Phase 3.

In Amendment 8, the total number of participants enrolled from the US in Stage 3 will be revised to the correct number enrolled (162 from South Africa/UK and 54 from the US). Furthermore, because of the additional enrolled participants from the US in protocol amendment 7, the duration of the study has increased from approximately 48 months to approximately 60 months.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary Objectives and Endpoints

3.1.1. Primary Objectives: Stage 1

- To describe the safety and tolerability of various GBS6 formulations in healthy nonpregnant women 18 to 40 years of age.
- To describe the safety and tolerability of a booster dose of GBS6 when administered to healthy nonpregnant women.

3.1.2. Primary Endpoints: Stage 1

- Proportions of nonpregnant women reporting prompted local reactions within 7 days following administration of the primary and booster doses of investigational product (pain at the injection site, redness, and swelling).
- Proportions of nonpregnant women reporting prompted systemic events within 7 days following administration of the primary and booster doses of investigational product (fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain).
- Proportions of nonpregnant women reporting adverse events (AEs) through 1 month following administration of the primary and booster doses of investigational product.
- Proportions of nonpregnant women reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) through 6 months following administration of the primary dose and approximately 7 to 12 months following the booster dose of investigational product.

3.1.3. Primary Objectives: Stage 2

- To describe the safety and tolerability of various GBS6 formulations when administered to healthy pregnant women 18 to 40 years of age vaccinated at 27 to 36 weeks' gestation.

- To assess the safety of maternal immunization in infant participants born to women who were vaccinated with various GBS6 formulations during pregnancy.

3.1.4. Primary Objectives: Stage 3

- To describe the safety and tolerability of 1 selected dose/formulation of GBS6 when administered to healthy pregnant women 18 to 40 years of age vaccinated at 24 to 36 weeks' gestation.

- To assess the safety of maternal immunization in infant participants born to women 18 to 40 years of age who were vaccinated with 1 selected dose/formulation during pregnancy.

3.1.5. Primary Safety Endpoints (Maternal Participants): Stages 2 and 3

- Proportions of sentinel-cohort maternal participants (Stage 2 only) with clinical laboratory abnormalities following administration of investigational product at the 2-week follow-up visit.

- Proportions of maternal participants reporting prompted local reactions within 7 days following administration of investigational product (pain at the injection site, redness, and swelling).

- Proportions of maternal participants reporting prompted systemic events within 7 days following administration of investigational product (fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain).

- Proportions of maternal participants reporting AEs through 1 month after administration of investigational product.

- Proportions of maternal participants with SAEs, MAEs, and obstetric complications (prepartum, intrapartum, and postpartum) throughout the study (Visit 1 through the 12-month postdelivery study visit).

- Proportions of maternal participants with each delivery outcome (live birth, delivery mode).

3.1.6. Primary Safety Endpoints (Infant Participants): Stages 2 and 3

- Proportions of infant participants with specific birth outcomes.
- Proportions of infant participants with AEs from birth to 6 weeks of age.
- Proportions of infant participants with SAEs, AEs of special interest (major congenital anomalies, developmental delay, and suspected or confirmed GBS infection), and MAEs through 12 months of age.

3.2. Secondary Objectives and Endpoints

3.2.1. Secondary Objectives: Stage 1

- To describe the immunogenicity of various GBS6 formulations when administered to healthy nonpregnant women.
- To describe the immunogenicity of a booster dose of GBS6 when administered to healthy nonpregnant women.

3.2.2. Secondary Objective: Stage 2

- To describe the immunogenicity of various GBS6 formulations when administered to healthy pregnant women.

3.2.3. Secondary Objective: Stage 3

- To describe the immunogenicity of 1 selected dose level/formulation of GBS6 when administered to healthy pregnant women.

3.2.4. Secondary Objectives: Stages 2 and 3

- To describe GBS6 antibody levels in infant participants delivered to maternal participants vaccinated with GBS6.
- To assess placental transfer of antibody from maternal participants vaccinated with GBS6 to their infant participants.

3.2.5. Secondary Endpoints: Stage 1

- GBS serotype-specific IgG geometric mean concentrations (GMCs) 1 month after vaccination in nonpregnant women.
- GBS serotype-specific IgG geometric mean concentrations (GMCs) measured before and 1 month, 3 months, and 6 months after a booster vaccination in nonpregnant women.

3.2.6. Secondary Endpoints (Maternal Participants): Stages 2 and 3

- GBS serotype-specific IgG GMCs measured at 2 weeks and 1 month after vaccination and at delivery in maternal participants.
- GBS serotype-specific OPA geometric mean titers (GMTs) measured 1 month after vaccination and at delivery in maternal participants.

3.2.7. Secondary Endpoints (Infant Participants): Stages 2 and 3

- GBS serotype-specific IgG GMCs in infant participants measured at birth.
- GBS serotype-specific OPA GMTs in infant participants measured at birth.

3.3. Exploratory Objectives and Endpoints

3.3.1. Exploratory Objectives: Stage 1

CCI [redacted]

3.3.2. Exploratory Objectives: Stages 2 and 3

CCI [redacted]

3.3.3. Exploratory Objective: Stages 1, 2, and 3

CCI [redacted]

3.3.4. Exploratory Endpoints: Stage 1

3.3.5. Exploratory Endpoints (Maternal Participants): Stages 2 and 3

3.3.6. Exploratory Endpoints (Infant Participants): Stages 2 and 3

4. STUDY DESIGN

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of a multivalent GBS vaccine in healthy 18- to 40-year-old nonpregnant women as well as pregnant women and their infants. Participants in Stage 2 will be vaccinated between 27 0/7 and 35 6/7 weeks' gestation and participants in Stage 3 will be vaccinated between 24 0/7 and 35 6/7 weeks' gestation.

4.1. Diversity of Study Population

This study has already completed enrollment in South Africa/UK and an additional 54 participants will be enrolled in the US, where the diversity strategy will include high-performing sites with the potential to support the recruitment of diverse populations. The diversity strategy for this study will include the following:

- Selecting sites that have access to diverse participants within their locales.
- Educating sites about the importance of increasing diversity on clinical trials and Pfizer's commitment.
- Investigator site recruitment plans that are cocreated with and include diverse recruitment tools and information to support enrollment.
- Real-world data are used to target outreach and potential referring physicians.
- Continual monitoring of diverse enrollment to identify additional opportunities to include diverse populations.

4.2. Stage 1

Nonpregnant women in good health will be screened, enrolled, and randomized in a 1:1:1 ratio (approximately 22 participants enrolled/group) to receive placebo (saline control) or GBS6 (20 µg CPS/serotype/dose) with or without $AlPO_4$. Participants will have blood drawn prior to vaccination (Visit 1), 2 weeks after vaccination (Visit 2), and 1 month after vaccination (Visit 3). E-diaries will be used to collect prompted local reaction and systemic event data for 7 days after vaccination. AEs will be collected through 1 month after vaccination (Visit 3). In addition, MAEs and SAEs will be collected from screening through 6 months after vaccination (Visit 4). A Pfizer IRC and an external data monitoring committee (EDMC) will review the 1-month postvaccination safety data (unblinded) from Stage 1 and the 1-month safety and immunogenicity data from the various GBS6 formulations from the FIH Phase 1/2 study before progression into Stage 2.

If a dose level or formulation does not demonstrate the expected 1-month immunogenicity in the FIH Phase 1/2 study (C1091001) or acceptable safety profile in Stage 1 of this Phase 1/2 study, that dose level or formulation will not be evaluated in Stage 2.

The study will proceed to Stage 2 at the discretion of the IRC in consultation with the EDMC.

Stage 1 participants (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 approximately 2 years after the primary dose of investigational product. Participants will have blood drawn at the prebooster screening visit, prior to the booster vaccination (Visit 6), 1 month after the booster vaccination (Visit 7), 3 months after the booster vaccination (Visit 8), 6 months after the booster vaccination (Visit 9), and at the blood draw follow-up visit after the booster vaccination (Visit 10).

E-diaries will be used to collect prompted local reaction and systemic event data for 7 days after the booster vaccination. AEs will be collected through 1 month after vaccination (Visit 7). In addition, MAEs and SAEs will be collected from the booster vaccination visit (Visit 6) through approximately 7 to 12 months after the booster vaccination (Visit 10).

4.3. Stage 2

Stage 2 will utilize a sentinel-cohort design, with cohort progression and dose escalation taking place after a safety review (data from each maternal participant through 14 days after vaccination) of the sentinel cohort of participants at each dose level (see Table 1). Upon providing informed consent, pregnant women will be enrolled and screened for general health, health of the pregnancy, and GA. Pregnant women, once consented, will be referred to as "maternal participants." The first 42 eligible maternal participants at each dose level will be referred to as the sentinel cohort. Starting with the lowest dose level, maternal participants will be randomly assigned (1:1:1 ratio, 14 participants per group) to receive a single dose of GBS6, formulated with or without $AlPO_4$, or placebo (saline control) within the sentinel cohort of a given dose level. The enrollment rate in the sentinel cohort will be limited to a maximum of 5 participants per day. A review of the 14-day safety data in a sentinel cohort will be conducted by the Pfizer IRC, and if deemed acceptable, will trigger:

- enrollment in the expanded cohort at that dose level (1:1:1 ratio, 26 participants per group), with no prespecified limit on daily enrollment until approximately 78 additional maternal participants are enrolled (see Table 2), and
- enrollment in the sentinel cohort for the next higher dose level (see Table 2).

Enrollment will proceed this way in a staggered fashion through the highest dose level. Approximately 360 maternal participants are planned to be enrolled into Stage 2.

This study will use stopping rules for the sentinel cohort, and 1 stopping rule (serious, unexpected AE considered possibly related to vaccine) will also apply to the expanded-cohort enrollment phase. Stopping rules (and the decision to terminate or restart at a given dose level) may be applied independently for each formulation at the discretion of the Pfizer IRC in conjunction with the EDMC recommendations (therefore, it is possible that after a stopping rule is met at a given dose level, one formulation [with or without $AlPO_4$] may proceed while the other may not).

The IRC will meet after each interim analysis to review safety and immunogenicity data, and on an ad hoc and timely basis to review safety data if a stopping rule is triggered, and to make recommendations for the study. In addition to the ad hoc meetings convened in the case a stopping rule is met, the EDMC will also meet periodically to conduct routine reviews of safety data.

When all Stage 2 sentinel-cohort maternal participants and their infant participants have completed the delivery/birth visit, safety and immunogenicity data will be unblinded and reviewed, when available, by the IRC for Pfizer informational and planning purposes. For details of sponsor blinding, refer to Section 6.8.

When all Stage 2 maternal participants and their infant participants have completed the delivery/birth visit, safety and immunogenicity data will be unblinded by group, when available, analyzed, and reviewed by the Pfizer IRC. The final GBS6 dose and formulation to take into Stage 3 and further development will be selected after this review. For details of sponsor blinding, refer to Section 6.8.

4.4. Stage 3

Approximately 216 additional maternal participants will be enrolled into Stage 3 (approximately 162 from South Africa/UK and 54 from the US) to receive a single dose/formulation of the selected GBS6 or placebo (saline control) in a 1:1 ratio. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks. There will be no dose escalation, no sentinel cohorts, and no planned stopping rules. The visit schedule, follow-up, and assessments for maternal participants and their infant participants will be similar to those in Stage 2. The additional data from Stage 3 will contribute to the safety database of maternal participants to support the design of the Phase 3 program.

When Stage 3 maternal participants and their infant participants have completed the delivery/birth visit, safety and immunogenicity data will be unblinded by group, when available, and analyzed and reviewed by the Pfizer IRC.

Table 1. Enrollment and Dose Escalation Design

Dose Escalation		Stage 1 Nonpregnant Women	Stage 1 Safety Data Review by Pfizer IRC and EDMC[a]	Stage 2 Maternal Participants							Stage 2 Safety and Immunogenicity Review/Dose Selection	Stage 3 Maternal Participants
Lowest Dose	- GBS6 lowest dose with $AlPO_4$ - GBS6 lowest dose without $AlPO_4$ - Placebo (saline control)			Enroll sentinel cohort (n=42)	14-Day safety review by IRC	Complete enrollment of expanded[b] cohort(n=78)						Enroll and vaccinate (n=216 GBS6 selected[c] or placebo (saline)
Middle Dose	- GBS6 middle dose with $AlPO_4$ - GBS6 middle dose without $AlPO_4$ - Placebo (saline control)					Enroll sentinel cohort[b] (n=42)	14-Day safety review by IRC	Complete enrollment of expanded cohort[b] (n=78)				
Highest Dose	- GBS6 highest dose with $AlPO_4$ - GBS6 highest dose without $AlPO_4$ - Placebo (saline control)	Enroll and vaccinate[d] (n=66)						Enroll sentinel cohort[b] (n=42)	14-Day safety review by IRC	Complete enrollment of expanded cohort (n=78)		

Abbreviations: $AlPO_4$ = aluminum phosphate; CPS = capsular polysaccharide; EDMC = external data monitoring committee; FIH = first-in-human; IRC = internal review committee.

a. Safety and immunogenicity data at the 1-month postvaccination time point from the US FIH Phase 1/2 study (C1091001) will also be included in the review.
b. The 14-day safety review by the IRC will trigger enrollment of the expanded cohort (at the same dose level) and sentinel cohort (for the next dose level).
c. One of the 6 GBS6 dose levels with or without $AlPO_4$.
d. Nonpregnant women will receive the 20-µg CPS/serotype/dose (with or without $AlPO_4$) of GBS6. Stage 1 participants (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 (20 µg CPS/serotype/dose with $AlPO_4$) approximately 2 years after the primary dose of investigational product.

4.5. Duration of Participant Participation

Each participant will participate in the study for approximately 6 to 12 months for Stage 1 (nonpregnant women) and up to 16 months for Stages 2 and 3 (pregnant women and their infant participants). Stage 1 participants (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 approximately 2 years after the primary dose of investigational product and will participate for additional visits through approximately 12 months.

4.6. Duration of Study

The study duration will be approximately 60 months.

4.7. Number of Participants

Refer to Table 2 below for a detailed description of the number of participants per stage and dose/formulation group. Participants who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal. A total of approximately 642 participants (66 nonpregnant women and 576 maternal participants and their infant participants) will be enrolled in this study by central randomization.

4.7.1. Stage 1

Approximately 66 participants (nonpregnant women) will be enrolled into Stage 1, 22 participants at each formulation of GBS6 (with/without $AlPO_4$) and 22 participants in the placebo group. Stage 1 participants (nonpregnant women) will receive a booster dose of GBS6 (20 µg CPS/serotype/dose with $AlPO_4$) approximately 2 years after initial investigational product administration.

4.7.2. Stage 2

Approximately 360 maternal participants will be enrolled into Stage 2. The first 42 participants within a dose level (low, middle, high) will compose the sentinel cohort with 14 participants at each dose/formulation and 14 participants in the placebo group. The enrollment rate in each of the sentinel cohorts will be limited to a maximum of 5 participants per day. Further enrollment will be expanded at each dose level until 78 additional participants are enrolled (expanded cohort).

4.7.3. Stage 3

Approximately 216 maternal participants will be enrolled into Stage 3 (approximately 162 from South Africa/UK and 54 from the US), 108 at the selected GBS6 dose/formulation and 108 in the placebo group. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks.

Table 2. Planned Participants: Total and Number in Each Stage and Group

Stage 1 Dose/Formulation Group[a]		Total (1:1:1)		
Highest Dose[b]	GBS6 (20 µg CPS/serotype/dose) with $AlPO_4$	22		
	GBS6 (20 µg CPS/serotype/dose) without $AlPO_4$	22		
	Placebo (saline control)	22		
Stage 2 Dose/Formulation Groups		**Sentinel (1:1:1)**	**Expanded (1:1:1)**	**Total**
Lowest Dose	GBS6 lowest dose with $AlPO_4$	14	26	40
	GBS6 lowest dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[c]
Middle Dose	GBS6 middle dose with $AlPO_4$	14	26	40
	GBS6 middle dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[c]
Highest Dose	GBS6 highest dose with $AlPO_4$	14	26	40
	GBS6 highest dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[c]
Stage 3 Dose/Formulation Group		**Total (1:1)**		
Selected Dose	Selected GBS6 dose/formulation	108		
	Placebo (saline control)	108		

Abbreviations: $AlPO_4$ = aluminum phosphate; CPS = capsular polysaccharide; FIH = first-in-human.

a. Stage 1 participants (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 (20 µg CPS/serotype/dose with $AlPO_4$) approximately 2 years after the primary dose of investigational product.
b. One hundred four healthy adults (males and females) 18 to 49 years of age have received this dose level (~52/formulation with/without $AlPO_4$) in the US FIH Phase 1/2 study (C1091001).
c. Approximately 120 pregnant control participants receiving placebo (saline control) in total in Stage 2.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse population including, where permitted under local regulations, age, sex, race, and ethnicity. 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.

Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled into the study. The enrollment approval process will be initiated for a participant after an informed consent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment approval will be based on review of CRF/system data.

5.1. Inclusion Criteria – Stage 1

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

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the participant has been informed of all pertinent aspects of the study.

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

3. Healthy **nonpregnant** females ≥18 to ≤40 years of age at enrollment who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

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

5. Negative urine pregnancy test at Visit 1 (prior to vaccination).

   Female participants of nonchildbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

   All other female participants (including female participants with tubal ligations) are considered to be of childbearing potential.

6. Documented negative HIV, hepatitis C virus (HCV), and acute or chronic hepatitis B virus (HBV) infection at screening.

5.2. Inclusion Criteria – Stage 1 Booster Vaccination

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

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the participant has been informed of all pertinent aspects for the booster vaccination and subsequent visits.

2. Participant must have received investigational product at Visit 1.

3. Willing and able to comply with scheduled visits, investigational plan, laboratory tests, and other study procedures, including completion of the e-diary from Day 1 to Day 7 following booster vaccination with GBS6.

4. Participant continues to meet all Stage 1 inclusion criteria and none of the Stage 1 exclusion criteria **(except exclusion criterion 11)**.

5. Healthy nonpregnant female determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for booster vaccination and received investigational product at Visit 1.

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

7. Negative urine pregnancy test at Visit 6 (prior to vaccination).

Female participants of nonchildbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

All other female participants (including female participants with tubal ligations) are considered to be of childbearing potential.

8. Documented negative HIV, hepatitis C virus (HCV), and acute or chronic hepatitis B virus (HBV) infection at screening.

5.3. Exclusion Criteria – Stage 1

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

1. 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 participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

2. Participation in other studies involving investigational drug(s), vaccines, or medical devices within 28 days prior to study entry and/or during study participation.

3. Other 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.

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

5. History of microbiologically proven invasive disease caused by GBS (*S agalactiae*).

6. Immunocompromised participants with known or suspected immunodeficiency.

7. Participants who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt through the 1-month postvaccination blood draw. 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.

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

9. Any known or suspected autoimmune or neuroinflammatory disease (refer to the study reference manual [SRM]).

10. Current alcohol abuse or illicit drug use.

11. Previous vaccination with any licensed or investigational GBS vaccine (other than GBS6 received as a primary vaccination at Visit 1), or planned receipt during the participant's participation in the study (through the last blood draw).

12. Vaccination with diphtheria- or CRM_{197}-containing vaccine(s) from 6 months before investigational product administration.

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

14. Female participants who are breastfeeding.

15. Participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for at least 3 months after administration of the investigational product.

5.4. Inclusion Criteria – Stages 2 and 3 – Maternal Participants

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

1. Evidence of a personally signed and dated ICD indicating that the participant has been informed of all pertinent aspects of the study.

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

3. Healthy females ≥18 and ≤40 years of age who are ≥27 0/7 (Stage 2) or ≥24 0/7 (Stage 3) to ≤35 6/7 weeks' gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, and at no increased risk for complications and no significant fetal abnormalities observed on ultrasound performed at any time prior to study entry and/or at the screening visit.

   Gestational age (GA) will be documented based on one of the following composite criteria based on timing and availability of data on the last menstrual period (LMP), ultrasound, and physical examination. The earliest ultrasound data available during the current pregnancy should be used to establish GA:

   a. **First-Trimester Data Available** (data obtained at ≤13 6/7 weeks):

      - The date of the first day of the reported LMP may be used to establish the GA if corroborated by a first-trimester ultrasound.

      - If there is a discrepancy of >7 days between the LMP-determined GA and a first-trimester ultrasound OR the LMP is uncertain/unknown, then the GA should be determined using the first-trimester ultrasound.

   b. **Second-Trimester Data Available** (data obtained at 14 0/7 to 27 6/7 weeks):

      - The date of the first day of the reported LMP may be used to establish the GA if corroborated by a second-trimester ultrasound or a physical examination including fundal height.

      - If there is a discrepancy of >10 days between the LMP-determined GA and the second-trimester ultrasound OR if the LMP is uncertain/unknown, then the GA should be determined using the second-trimester ultrasound.

c. **Third-Trimester Data Available** (data obtained at ≥28 weeks):

- The date of the first day of the reported LMP may be used to establish the GA if corroborated by a third-trimester ultrasound.
- If there is a discrepancy of >21 days between the LMP-determined GA and the third-trimester ultrasound OR if the LMP is uncertain/unknown, then the GA should be determined using the third-trimester ultrasound.

4. Pregnant participants must be receiving prenatal standard of care at the clinics/physician offices/hospital network affiliated with the clinical study site.

5. Determined by medical history, physical examination, screening laboratory assessment, and clinical judgment to be appropriate for inclusion in the study.

6. Expected to be available for the duration of the study, can be contacted by telephone during study participation, and expected to give informed consent for their infant participant to participate in the study.

7. Documented negative HIV antibody, HBV surface antigen, HCV antibody, and syphilis tests at screening.

5.5. Exclusion Criteria – Stages 2 and 3 – Maternal Participants

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

1. 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 participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

2. Participants whose unborn baby have been fathered by investigational site staff members directly involved in the conduct of the study or their family members, site staff members otherwise supervised by the investigator, or Pfizer employees directly involved in the conduct of the study.

3. **For Stage 2 sentinel-cohort participants only,** laboratory test results at the screening visit outside the normal reference range for pregnant women according to their trimester in pregnancy.

4. Participation in other studies involving investigational drug(s), vaccines, or medical devices within 28 days prior to study entry and/or during study participation.

5. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the investigational product or any related vaccine.

6. History of microbiologically proven invasive disease caused by GBS (*S agalactiae*), or history of an infant with GBS disease.

7. Current alcohol abuse or illicit drug use.

8. Prepregnancy body mass index (BMI) of ≥40 kg/m^2. If prepregnancy BMI is not available, the BMI at the time of the first obstetric visit during the current pregnancy may be used.

9. Clinical history of primary genital herpes simplex virus (HSV) infection during the current pregnancy.

10. Participants with known or suspected immunodeficiency.

11. 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 postvaccination blood draw. 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.

12. Other 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.

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

14. Previous vaccination with any licensed or investigational GBS vaccine, or planned receipt during study participation.

15. Vaccination with diphtheria- or CRM_{197}-containing vaccine, from 6 months before investigational product administration. Licensed Tdap may be given as per local recommendation for immunization in pregnant women, provided that it is administered at a minimum 15 days before or after study vaccination (see temporary delay conditions in the protocol, Section 5.8.1).

16. Receipt of blood/plasma products or immunoglobulin, from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, anti-D immunoglobulin (eg, RhoGAM), which can be given at any time.

17. A prior history of or current pregnancy complications or abnormalities that will increase the risk associated with the participant's participation in, and completion of, the study, including but not limited to the following (refer to the SRM) for further details):

    - Gestational hypertension or preeclampsia-eclampsia
    - Placental abnormality
    - Polyhydramnios or oligohydramnios
    - Significant bleeding or blood clotting disorder
    - Gestational diabetes
    - Any signs of premature labor with the current pregnancy
    - Prior stillbirth or neonatal death, prior low-birth-weight or preterm delivery, prior history of at least 3 miscarriages, prior pregnancies numbering greater than 5, or previous infant with a known genetic disorder or major congenital anomaly
    - Confirmed GBS bacteriuria during the current pregnancy

18. Major illness of the mother or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the participant's participation in, and completion of, the study or could preclude the evaluation of the participant's response.

19. Any known or suspected autoimmune or neuroinflammatory disease (refer to the SRM).

5.6. Inclusion Criteria – Infant Participants – Stages 2 and 3

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

1. Evidence of a signed and dated ICD signed by the parent(s).

   The maternal participant must participate in the informed consent process and sign and date an ICD for herself and her fetus/infant prior to the maternal participant's taking part in the study. Informed consent will be obtained from the father of the fetus/infant if mandated by local requirements.

2. Parent(s) willing and able to comply with scheduled visits, investigational plan, laboratory tests, and other study procedures.

5.7. Exclusion Criteria – Infant Participants – Stages 2 and 3

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

1. Infant who is a direct descendant (eg, child or grandchild) of the study personnel.

5.8. Temporary Delay Criteria (Stages 1, 2, and 3)

The following conditions are temporary or self-limiting and a participant may be vaccinated 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 and Visit 6 [Stage 1 only]).

5.8.1. Criteria for Temporarily Delaying Vaccine Administration (Stages 1, 2, and 3)

- Current febrile illness (body temperature ≥38°C [≥100.4°F]) or other acute illness within 48 hours before investigational product administration.
- Receipt of any inactivated 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.

5.9. Lifestyle Requirements

5.9.1. Contraception (Stage 1 Participants Only)

All female participants who are of childbearing potential and are sexually active with 1 or more members of the opposite sex must agree to use a highly effective method of contraception consistently and correctly for at least 3 months after administration of investigational product. 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 from the permitted list of contraception methods (see below) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or the partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the participant plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

5.10. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number if they later meet eligibility criteria.

5.11. 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 study 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.

6. INVESTIGATIONAL PRODUCTS

For the purposes of this study, and per International Council for Harmonisation[62] (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product(s) are GBS6 (containing CCI µg CPS/serotype/dose, each formulated with or without $AlPO_4$) and placebo (saline control). Participants will receive 1 dose of either GBS6, with or without $AlPO_4$, or placebo (saline control) at Visit 1 administered intramuscularly by CCI, preferably of the nondominant arm. The dose level/formulation received by each participant will be based on which stage of the study the participant will be enrolled in (see Table 1).

In Stage 1, 1 dose level (20 µg CPS/serotype/dose), with or without $AlPO_4$, will be used. The booster vaccination for Stage 1 will be 1 dose level (20 µg CPS/serotype/dose with $AlPO_4$). **In Stage 2,** up to 6 dose level/ formulations of GBS6 may be used (3 dose levels, each formulated with or without $AlPO_4$). The number of dose level/formulations evaluated in Stage 2 will be influenced by safety and immunogenicity data from the US FIH Phase 1/2 study (C1091001). **In Stage 3,** 1 dose level/formulation will be evaluated after a review of safety and immunogenicity data from Stage 2.

See Table 3 for more information on the investigational product dose level/formulation groups.

6.1. Investigational Product Supplies

GBS6 and placebo (saline control) will be provided by the sponsor to each study site.

Study vaccines will be packed and labeled as investigational product in accordance with current guidelines and applicable local and legal regulatory requirements. The formulation of the investigational products is described below.

6.1.1. Dosage Form(s) and Packaging

GBS6 is composed of serotypes Ia, Ib, II, III, IV, and V CPS CCI

There are 3 dose levels (CCI), each formulated either with $AlPO_4$, CCI, or without $AlPO_4$. See Table 3 for further details.

Table 3. Target Composition of the GBS6 Formulations Intended for Clinical Evaluation

CCI [redacted]

GBS6 formulated with or without $AlPO_4$ is supplied as a sterile preservative-free solution (without $AlPO_4$) or suspension (with $AlPO_4$) CCI [redacted]

The placebo will be a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose) and will be provided by the sponsor to each study site. The placebo will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.

6.1.2. Preparation and Dispensing

Investigational product preparation and dosing information will be provided in the investigational product manual (IPM).

GBS6 and placebo will be prepared by qualified unblinded site personnel according to the IPM. The investigational product will be administered by qualified unblinded site personnel who keep the participants blinded, because of the difference in investigational product appearance, ie, cloudy for GBS6 with $AlPO_4$ versus clear for GBS6 without $AlPO_4$ and placebo (saline control).

The investigational product will be assigned using an interactive response technology (IRT) drug management system at Visit 1. The IRT system will assign participants a unique container number from the system, which will be printed on the carton and the vial within the carton. Qualified unblinded personnel will dispense the assigned investigational product for preparation and administration.

Please refer to the IPM for instructions on how to prepare the investigational product for administration.

6.2. Allocation to Investigational Product

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

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

Stage 1 participants and maternal participants (Stages 2 and 3) will be allocated to an investigational product group as described above. Infants (infant participants) of the maternal participants will be assigned a participant number at birth. Since the booster vaccination for Stage 1 participants is open label, the IRT system will be used to allocate the container number.

6.3. Participant Compliance

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

6.4. Administration

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.

Preparation and administration of investigational products should be performed by an appropriately qualified, 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).

In Stage 1, participants will receive 1 dose of either GBS6, formulated with or without $AlPO_4$, or placebo (saline control) at Visit 1 in accordance with the study's schedule of activities. All returning participants in Stage 1 will also receive 1 dose of GBS6 (20 µg CPS/serotype/dose with $AlPO_4$) at Visit 6 in accordance with the study's schedule of activities. Stage 2 participants will receive 1 of 3 possible dose levels of GBS6, formulated with or without $AlPO_4$, or placebo (saline control) at Visit 1 in accordance with the study's schedule of activities.

In Stage 3, participants will receive 1 selected dose/formulation of either GBS6 or placebo (saline control) at Visit 1 in accordance with the study's schedule of activities.

GBS6 or placebo (saline control) should be administered intramuscularly by CCI [redacted], preferably of the nondominant arm.

6.5. Investigational Product Storage

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.

Study interventions should be stored in their original containers.

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.

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.

Any storage conditions stated in the SRSD (GBS6 IB) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product 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. Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site in the IPM.

6.6. Investigational Product Accountability

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

6.6.1. Destruction of Investigational Product Supplies

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

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.7. Blinding of the Site Personnel

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

The booster vaccination at Visit 6 for Stage 1 participants will be open label.

6.8. Blinding of the Sponsor

In each stage of the study, sponsor study team members will remain blinded to vaccine assignment of all participants enrolled in that stage, following the principles outlined in ICH E9 guideline on Statistical Principles for Clinical Trials, Section 2.3.1,[62] until the planned interim analyses in that stage. Four unblinded interim analyses are planned in the study (refer to Section 10.4). For the second interim analysis, the study team will only be unblinded for the sentinel-cohort data and will remain blinded for all expanded cohorts. In an event that unblinded results need to be submitted for regulatory communications prior to study team unblinding, efforts will be made to ensure study team members involved in participant assessments are blinded.

Certain sponsor personnel not directly involved in the conduct of the study will review unblinded data as defined in an IRC charter per Pfizer standard operating procedures (SOPs). Unblinded sponsor personnel who are not part of the study team will be assigned to assess whether a stopping rule is triggered for ongoing safety review as well as to work with an independent statistical team center for IRC review activities. Laboratory personnel performing the immunologic assays will remain blinded to vaccine assigned/received throughout the study.

The booster vaccination at Visit 6 for Stage 1 participants will be open label.

6.9. Breaking the Blind

The study will be participant and investigator blinded, except for the open-label booster vaccination given at Visit 6 for Stage 1 participants.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

6.10. Concomitant Treatment(s)

6.10.1. Prohibited Nonstudy Vaccines and Medications During the Study

6.10.1.1. Stage 1

- 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).

6.10.1.2. Stages 2 and 3 – Maternal Participants

- 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 (except anti-D immunoglobulin, eg, RhoGAM, which can be given at any time), 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).

6.10.2. Permitted Nonstudy Vaccines and Medications During the Study

6.10.2.1. Stage 1

- 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 prior to vaccination or the day of the investigational product administration.

- Any concomitant vaccines required by local recommendations and permitted by the protocol may be administered concomitantly with GBS6 or placebo (saline control) but must be administered in a different limb.

6.10.2.2. Stages 2 and 3 – Maternal Participants

- Licensed influenza vaccine, tetanus vaccines, and tetanus diphtheria vaccines may be given during the study starting 15 days after investigational product administration as per local recommendation for immunization in pregnant women. 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 prior to vaccination or the day of the investigational product administration.

- Any concomitant vaccines required by local recommendations and permitted by the protocol may be administered concomitantly with GBS6 or placebo (saline control) but must be administered in a different limb.

The standard of care for prevention of GBS disease in infants will be applicable to all pregnant women enrolled in the study in accordance with local recommendations/guidelines.

6.10.2.3. Stages 2 and 3 – Infant Participants

- Any routine vaccination given as part of the national recommended vaccination schedule for infants will be administered.

6.10.3. Recording Nonstudy Vaccinations and Concomitant Medications

6.10.3.1. Stage 1

The name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD to Visit 3 (1-month follow-up visit) will be collected and recorded in the CRF. For participants receiving the booster vaccination, the name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD (Visit 5) to Visit 7 (1-month booster vaccination follow-up) will be collected and recorded in the CRF.

Any medications taken from the signing of ICD through Visit 3 (1-month follow-up visit) will be recorded in the CRF. Additionally, any medication taken to treat AEs from the signing of the ICD through Visit 4 will be recorded in the CRF. For participants receiving the booster vaccination, medications taken from the signing of ICD (Visit 5) through Visit 7 (1-month booster vaccination follow-up) will be collected and recorded in the CRF. Additionally, any medication taken to treat AEs from the signing of the ICD (Visit 5) through Visit 10 will be recorded in the CRF.

6.10.3.2. Stages 2 and 3 – Maternal Participants

The name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD to Visit 4 (delivery) will be collected and recorded in the CRF.

Any medications taken from the signing of the ICD through Visit 3 (1-month follow-up visit) will be recorded in the CRF. Antibiotic treatment taken from the signing of the ICD to Visit 9 (12-month postdelivery follow-up) will be recorded. Additionally, any medication taken to treat AEs from the signing of the ICD through Visit 9 will be recorded in the CRF.

6.10.3.3. Stages 2 and 3 – Infant Participants

The name and date of administration for all nonstudy vaccinations received from Visit 1 (birth) to Visit 7 (12-month postdelivery follow-up) will be collected and recorded in the CRF.

Any medications taken from Visit 1 (birth) through Visit 3 (6-week postdelivery follow-up) will be recorded in the CRF. Antibiotic treatment taken from birth to Visit 7 (12-month postdelivery follow-up) will be recorded. Additionally, any medication taken to treat AEs from birth through Visit 7 will be recorded in the CRF.

7. STUDY PROCEDURES

The schedule of procedures is summarized in the schedule of activities. The day of vaccination is considered Day 1.

7.1. Stage 1 Study Procedures – Nonpregnant Women

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

7.1.1. Visit 0 – Screening (Days -7 to -2 Prior to Vaccination)

Participants will be screened from 2 to 7 days prior to administration of the investigational product to confirm that they meet eligibility (all of the inclusion and none of the exclusion) criteria for the study.

If the participant is found ineligible for the study on the basis of laboratory assessment, the investigator may advise the participant of the results by telephone, and the participant will be withdrawn from further participation in the study. All eligible participants (without laboratory abnormalities) will proceed to Visit 1.

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Assign a single participant identifier using the IRT system.

- Obtain and record the participant demography (including date of birth, sex, race, and ethnicity). The complete date of birth (dd-mmm-yyyy) 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.
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 5).
- Obtain a blood sample (approximately 5 mL) for HIV, HBV, and HCV testing. Participants testing positive for HIV, acute or chronic HBV, or HCV will not be eligible for randomization.
- Complete the source documents.
- Record nonstudy vaccinations and medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.1.2. Visit 1 – Vaccination (Day 1)

- Ensure that the participant continues to be eligible for the study, meets none of the participant withdrawal criteria as described in Section 7.5, and meets none of the temporary delay criteria as described in Section 5.8.
- Review screening laboratory results.
- Prior to vaccination, measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Prior to vaccination, perform a urine pregnancy test for female participants of childbearing potential.
- Prior to vaccination, collect a blood sample of approximately 15 mL for immunogenicity assessments.

- CCI [redacted]
- CCI [redacted] Refer to the SRM for further details.
- Verify understanding of and compliance with protocol requirements for contraception.
- A blinded site staff member will use the IRT system to obtain the participant's randomization number. An unblinded site staff member will use the IRT to assign investigational product container number and will prepare the investigational product and deliver it to the investigational product administrator. Please refer to the IPM for further instruction on this process.
- The unblinded administrator administers a single CCI [redacted], preferably of the nondominant arm.
- Blinded 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 a measuring device to measure local reactions and a digital thermometer for recording 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 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring ≥21 measuring device units [≥10.5 cm]).
- Remind participants that study staff may contact them to obtain additional information on Grade 3 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.
- Complete the participant's source documents.
- Record nonstudy vaccinations and concomitant medications as described in Section 6.10.3.

- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF, and an unblinded site staff member updates the investigational product accountability records.
- Designated site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

7.1.3. Visit 2 – 2-Week Follow-Up Visit (14-17 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 7.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- CCI [redacted]
- 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.
- Complete the participant's source documents.
- Record nonstudy vaccinations and medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.1.4. Visit 3 – 1-Month Follow-Up Visit (28-42 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 7.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- CCI [redacted]

- CCI [redacted] Refer to the SRM for further details.
- Complete the participant's source documents.
- Record nonstudy vaccinations and concomitant medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.1.5. Visit 4 – 6-Month Follow-Up Telephone Contact (160-200 Days After Visit 1)

The 6-month telephone contact should be attempted for all participants who have received vaccination, unless they have withdrawn consent. The following procedures will be performed:

- Verify understanding of and compliance with protocol requirements for contraception.
- Complete the participant's source documents.
- Record concomitant medications as described in Section 6.10.3. Only concomitant medication taken to treat an AE will be recorded in the CRF.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.1.6. Visit 5 – Pre-Booster Screening (Days -7 to -2 Prior to Booster Vaccination)

Participants will be screened from 2 to 7 days prior to the booster vaccination to confirm that they meet eligibility (all of the inclusion criteria and none of the exclusion criteria) for the booster vaccination.

If the participant is found ineligible on the basis of laboratory assessment, the investigator may advise the participant of the results by telephone, and the participant will be withdrawn from further participation in the study. All eligible participants (without laboratory abnormalities) will proceed to Visit 6.

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures, that have been diagnosed since Visit 1.

- 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.

- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 5).

- Obtain a blood sample (approximately 5 mL) for HIV, HBV, and HCV testing. Participants testing positive for HIV, acute or chronic HBV, or HCV will be withdrawn from further participation in the study.

- Collect an additional blood sample of approximately 25 mL.

- Complete the source documents.

- Record nonstudy vaccinations and concomitant medications as described in Section 6.10.3.

- Record AEs as described in Section 8.8 and Section 9.

- The investigator or an authorized designee completes the CRF.

7.1.7. Visit 6 – Booster Vaccination (Approximately 2 Years After Visit 1)

- Ensure that the participant is eligible for the booster vaccination and meets none of the temporary delay criteria as described in Section 5.8.

- Review screening laboratory results.

- Prior to vaccination, measure oral temperature.

- Prior to vaccination, perform a urine pregnancy test for female participants of childbearing potential.

- Prior to vaccination, collect a blood sample of approximately 140 mL.

- Verify understanding of and compliance with protocol requirements for contraception.

- Use the IRT to assign investigational product container number and prepare and administer a single [redacted], preferably of the nondominant arm. Please refer to the IPM for further instruction on this process.

- 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 a measuring device to measure local reactions and a digital thermometer for recording 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 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring ≥21 measuring device units [≥10.5 cm]).

- Remind participants that study staff may contact them to obtain additional information on Grade 3 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.

- Complete the participant's source documents.

- Record nonstudy vaccinations and concomitant medications as described in Section 6.10.3.

- Record AEs as described in Section 8.8 and Section 9.

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

- Designated site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

7.1.8. Visit 7 – 1-Month Booster Vaccination Follow-Up Visit (28-42 Days After Visit 6)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 140 mL.
- 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.
- Complete the participant's source documents.
- Record nonstudy vaccinations and concomitant medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.1.9. Visit 8 – 3-Month Booster Vaccination Follow-Up Visit (84-126 Days After Visit 6)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 140 mL.
- Complete the participant's source documents.
- Record concomitant medications as described in Section 6.10.3. Only concomitant medication taken to treat an AE will be recorded in the CRF.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.1.10. Visit 9 – 6-Month Booster Vaccination Follow-Up Visit (160-200 Days After Visit 6)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 140 mL.
- Complete the participant's source documents.
- Record concomitant medications as described in Section 6.10.3. Only concomitant medications taken to treat an AE will be recorded in the CRF.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.1.11. Visit 10 – Blood Draw Follow-Up Visit (14-184 Days After Visit 9)

- Obtain written informed consent before performing any study-specific procedures.
- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 125 mL.
- Complete the participant's source documents.
- Record concomitant medications as described in Section 6.10.3. Only concomitant medications taken to treat an AE will be recorded in the CRF.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.2. Stage 2 and 3 Study Procedures – Maternal Participants

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

7.2.1. Visit 0 – Screening (Days -14 to -2 Prior to Vaccination)

Participants will be screened from 2 to 14 days prior to administration of the investigational product to confirm that they meet eligibility (all of the inclusion and none of the exclusion) criteria for the study.

For Stage 2 sentinel-cohort participants only: In the 14-day screening period, retesting of the screening blood/chemistry laboratory parameters will be allowed at the discretion of the investigator if the investigator believes the results to be erroneous. In this circumstance, participants will return for a second screening visit within the 14-day screening period to reevaluate the screening laboratory parameters (see Section 7.2.2).

If the participant is found ineligible for the study on the basis of screening laboratory assessment and repeat testing is not warranted, the investigator may advise the participant of the results by telephone, and the participant will be withdrawn from further participation in the study. All eligible participants will proceed to Visit 1.

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Assign a single participant identifier using the IRT system.
- Obtain and record the participant demography (including date of birth, sex, race, and ethnicity). The complete date of birth (dd-mmm-yyyy) will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record current alcohol and tobacco usage.
- Obtain and record any medical and obstetric history of clinical significance including history from prior and current pregnancy(ies). Refer to the SRM for further details.
- Record the last normal menstrual period (LMP) and estimated date of delivery (EDD).
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- 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.
- Perform obstetric examination including but not limited to scars from previous deliveries, fundal height, fetal heart tones, and fetal movement.

- Perform obstetric ultrasound and/or record findings to confirm singleton pregnancy and rule out fetal abnormalities.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 5).
- Obtain blood sample (approximately 10 mL) for HBV, HCV, HIV, and syphilis testing. Participants testing positive for HIV, acute or chronic HBV, HCV, or syphilis will not be eligible for randomization.
- Stage 2 sentinel cohort only: Obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments. The following parameters will be assessed:
  - Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelets.
  - Blood chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
- Obtain urine sample for glucose and protein testing (urine dipstick).
- Complete the source documents.
- Record nonstudy vaccinations and medications (including antibiotic medications) as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.2.2. Visit 0 – Rescreening Visit (Days -14 to -2 Prior to Vaccination) – Stage 2 Sentinel-Cohort Participants Only

If abnormal blood/chemistry laboratory parameters are reported at Visit 0 and the investigator believes the results to be erroneous, a second screening visit may be conducted. The following information will be collected and the following assessments will be made at a rescreening visit:

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 5).
- Obtain a blood sample (approximately 10 mL) for analysis of hematology and blood chemistry assessments (see Section 8.5.3). Retest only abnormal laboratory parameters from Visit 0.

- Complete the source documents.
- Record nonstudy vaccinations and medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

If the participant is subsequently found ineligible for the study on the basis of hematology and/or blood chemistry laboratory assessment, the investigator may advise the participant of the results by telephone, and the participant will be withdrawn from further participation in the study. All eligible participants will proceed to Visit 1.

7.2.3. Visit 1 – Vaccination (Day 1) Visit

- Review laboratory results.
- Ensure that the participant continues to be eligible for the study, meets none of the participant withdrawal criteria as described in Section 7.5, and meets none of the temporary delay criteria as described in Section 5.8.
- Prior to vaccination, measure vital signs, including weight, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Obtain urine sample for glucose and protein testing (urine dipstick).
- Issue the participant an e-diary and provide instructions on its completion. Ensure that the participant records a baseline assessment of prompted systemic events in the e-diary prior to vaccination.
- Prior to vaccination, collect a blood sample of approximately 15 mL for immunogenicity assessments.
- CCI [redacted]
- CCI [redacted] Refer to the SRM for further details.

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

- The unblinded administrator administers a single CCI [redacted], preferably of the nondominant arm.

- Blinded 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 a measuring device to measure local reactions and a digital thermometer for recording daily temperatures and provide instructions on their use.

- Ask the participant to complete the e-diary from Day 1 to Day 7 (Day 1 is the day of vaccination).

- Ask the participant to contact the site staff or investigator immediately if prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring ≥21 measuring device units [≥10.5 cm]).

- Remind participants that study staff may contact them to obtain additional information on Grade 3 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.

- Complete the participant's source documents.

- Record nonstudy vaccinations and concomitant medications (including antibiotic medications) as described in Section 6.10.3.

- Record AEs as described in Section 8.8 and Section 9.

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

- Designated site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

7.2.4. Visit 2 – 2-Week Follow-Up Visit (14-17 Days After Visit 1)

If delivery occurs before this visit, this visit will not be conducted; however, the hematology and chemistry assessments planned to be collected at this visit should be conducted at the delivery visit, if possible. For the other procedures to be conducted at delivery, see Section 7.2.6.

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Measure vital signs, including weight, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- **Stage 2 sentinel cohort only:** Obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments. The following parameters will be assessed:
  - Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, and platelets.
  - Blood chemistries: ALT, AST, alkaline phosphatase, total bilirubin, BUN, and creatinine.
  - Retesting of abnormal laboratory parameters will be allowed at the discretion of the investigator if the investigator believes the results to be erroneous.
- 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.
- Complete the participant's source documents.
- Record nonstudy vaccinations and concomitant medications (including antibiotic medications) as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.2.5. Visit 3 – 1-Month Follow-Up Visit (28-42 Days After Visit 1)

If delivery occurs before this visit, please conduct the delivery visit instead. For procedures to be conducted at delivery, see Section 7.2.6.

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Measure vital signs, including weight, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- CCI [redacted]
- Complete the participant's source documents.
- Record nonstudy vaccinations and medications (including antibiotic medications) as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.2.6. Visit 4 – Delivery

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Record nonstudy vaccinations, any medication taken to treat AEs, and antibiotic medications as described in Section 6.10.3.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments. The blood sample may be collected up to 72 hours after delivery. Refer to the SRM for blood sample collection guidelines.

- CCI [redacted] Refer to the SRM for further details.
- Complete the participant's source documents.
- Record AEs as described in Section 8.8 and Section 9.
- Record pregnancy outcome information.
- The investigator or an authorized designee completes the CRF.

7.2.7. Visit 5 – 1-Week Postdelivery Follow-Up Telephone Contact (7-10 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5. This telephone contact should be performed by the investigator or a medically qualified member of the study site staff.
- Complete the participant's source documents.
- Record any medication taken to treat AEs and antibiotic medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.2.8. Visit 6 – 6-Week Postdelivery Follow-Up (35-49 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- CCI Refer to the SRM for further details.
- Complete the participant's source documents.
- Record any medication taken to treat AEs and antibiotic medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.2.9. Visit 7 – 14-Week Postdelivery Follow-Up (80-100 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Complete the participant's source documents.
- Record any medication taken to treat AEs and antibiotic medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.2.10. Visit 8 – 6-Month Postdelivery Follow-Up Telephone Contact (160-200 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Complete the participant's source documents.

- Record any medication taken to treat AEs and antibiotic medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.2.11. Visit 9 – 12-Month Postdelivery Follow-Up (365-385 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- Complete the participant's source documents.
- Record any medication taken to treat AEs and antibiotic medications as described in Section 6.10.3.
- Record AEs as described in Section 8.8 and Section 9.
- The investigator or an authorized designee completes the CRF.

7.3. Stage 2 and 3 Study Procedures – Infant Participants

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

7.3.1. Visit 1 – Delivery

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Assign a single participant identifier.
- Record demography (including date of birth, sex, race, and ethnicity) and available birth information, including but not limited to infant participant vital status (live, stillbirth, neonatal death), appearance, pulse, grimace, activity, and respiration (Apgar) score, birth length, birth weight, head circumference, and Ballard score. If the Ballard score is unavailable, it may be calculated and recorded up to 72 hours after delivery. The complete date of birth (dd-mmm-yyyy) will be collected to critically evaluate the antibody levels and safety profile by age.
- Record available vital signs, including axillary temperature, pulse rate, and respiratory rate.

- Record physical examination evaluating any clinically significant abnormalities within the following available body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.

- Collect a cord blood sample of approximately 10 mL for immunogenicity assessments. If cord blood is unavailable, a blood sample of approximately 2.5 mL may be collected in the infant participants up to 72 hours after delivery. Refer to the SRM for blood sample collection guidelines.

- Blood spot card collection will be performed using the cord blood sample, or blood draw (up to 72 hours after delivery) if cord blood is unavailable. Refer to the SRM for further details.

- CCI [redacted] Refer to the SRM for further details.

- Complete the participant's source documents.

- Record AEs as described in Section 8.8 and Section 9.

- Record nonstudy vaccines and concomitant medications (including antibiotic medications) as described in Section 6.10.3.

- The investigator or an authorized designee completes the CRF.

7.3.2. Visit 2 – 1-Week Postdelivery Follow-Up Telephone Contact (7-10 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.

- Collect and record breastfeeding information.

- Complete the participant's source documents.

- Record AEs as described in Section 8.8 and Section 9.

- Record nonstudy vaccines and concomitant medications (including antibiotic medications) as described in Section 6.10.3.

- The investigator or an authorized designee completes the CRF.

7.3.3. Visit 3 – 6-Week Postdelivery Follow-Up (35-49 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- 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; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Collect a blood sample of approximately 5 mL for immunogenicity assessments. Refer to the SRM for blood sample collection guidelines.
- CCI [redacted] Refer to the SRM for further details.
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 8.8 and Section 9.
- Record nonstudy vaccines and concomitant medications (including antibiotic medications) as described in Section 6.10.3.
- The investigator or an authorized designee completes the CRF.

7.3.4. Visit 4 – 14-Week Postdelivery Follow-Up (80-100 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- 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; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Collect a blood sample of approximately 5 mL for immunogenicity assessments. Refer to the SRM for blood sample collection guidelines.

- CCI [redacted] Refer to the SRM for further details.
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 8.8 and Section 9.
- Record nonstudy vaccines, any medication to taken treat AEs, and antibiotic medications as described in Section 6.10.3.
- The investigator or an authorized designee completes the CRF.

7.3.5. Visit 5 – 18-Week Postdelivery Follow-Up (119-133 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- 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; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Collect a blood sample of approximately 5 mL for assessment of antibody responses to routine pediatric vaccines (not required for infants born to US and UK Stage 3 participants). Refer to the SRM for blood sample collection guidelines.
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 8.8 and Section 9.
- Record nonstudy vaccines, any medication taken to treat AEs, and antibiotic medications as described in Section 6.10.3.
- The investigator or an authorized designee completes the CRF.

7.3.6. Visit 6 – 6-Month Postdelivery Follow-Up Telephone Contact (160-200 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 8.8 and Section 9.
- Record nonstudy vaccines, any medication taken to treat AEs, and antibiotic medications as described in Section 6.10.3.
- The investigator or an authorized designee completes the CRF.

7.3.7. Visit 7 – 12-Month Postdelivery Follow-Up (365-385 Days After Delivery)

- Ensure that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria as described in Section 7.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- 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; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Collect a blood sample of approximately 5 mL for assessment of antibody responses to routine pediatric vaccines (not required for infants born to US and UK Stage 3 participants). Refer to the SRM for blood sample collection guidelines.
- Collect and record breastfeeding information.
- Complete the participant's source documents.
- Record AEs as described in Section 8.8 and Section 9.
- Record nonstudy vaccines, any medication taken to treat AEs, and antibiotic medications as described in Section 6.10.3.
- The investigator or an authorized designee completes the CRF.

7.4. Unscheduled Visit (Stages 1, 2, and 3 – Maternal Participants)

If the participant reports redness or swelling at the injection site measuring ≥21 measuring device units (≥10.5 cm), fever ≥39.0°C (≥102.1°F), or severe injection site pain, severe nausea/vomiting, severe diarrhea, severe headache, severe fatigue/tiredness, severe muscle pain, or severe joint pain, a telephone contact must occur as soon as possible between the participant and the investigator or a medically qualified member of the study site staff to assess if an unscheduled visit is required. A site visit must be scheduled as soon as possible to assess the extent of the reaction unless:

- The participant is unable to attend the unscheduled visit.
- The reaction is no longer present at the time of the telephone contact.
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- 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.

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 8.5.2.
- 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 8.5.2.

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 headache, fatigue, muscle pain, joint pain, etc.) within 7 days after vaccination. Study staff may contact the participant to obtain additional information on Grade 3 events entered into the e-diary. Lastly, participants will be instructed to contact the site to report any significant illness, medical event, or hospitalization that occurs during the study period. The site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

7.5. Participant Withdrawal

An investigator and/or sponsor can withdraw a participant from the study if deemed appropriate. In addition, if a participant fails to continue to meet the inclusion criteria, new information becomes available that would exclude the participant, or the participant develops a condition or situation that would meet exclusion criteria (except exclusion criteria 11 and 12 [Stage 1] and exclusion criteria 14 and 15 [Stages 2 and 3] after Visit 1 relating to GBS6), the participant may be considered for withdrawal. Infant participants born from vaccinated maternal participants may be considered for withdrawal from study procedures for any medical condition(s) that, in the opinion of the investigator, would contraindicate blood sampling.

Reasons why a participant may discontinue or be withdrawn from the study include, but are not limited to, failure to meet entrance criteria (screening failure), AE, death, pregnancy (Stage 1 participants only), protocol violation, lost to follow-up, no longer willing to participate in the study, study terminated by sponsor, investigator declined further study participation, or any other reason. Participants who have received the investigational product will not be replaced regardless of the reason for withdrawal.

7.5.1. Withdrawal of Consent

After investigational product administration at Visit 1 and Visit 6 (Stage 1 only), participants (nonpregnant women in Stage 1; maternal participants, and parents of infant participants born to maternal participants in Stages 2 and 3) who request to discontinue further study procedures (eg, blood draws) at upcoming visits will be asked to remain in the study for protocol-specified safety follow-up procedures. The only exception to this is when a participant or parent specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. It is permissible that Visit 4 and Visit 10 (Stage 1 participants), Visit 9 (Stage 2 and 3 maternal participants), and Visit 7 (Stage 2 and 3 infant participants) be conducted via telephone contact for participants who are staying in the study for protocol-specified safety follow-up procedures only. 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 draws) 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.

7.6. Lost to Follow-Up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant as soon as possible to reschedule the missed visit, 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, make 3 telephone calls and, if necessary, send a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

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

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the participant to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant/participant's parent. All attempts to contact the participant/parent and information received during contact attempts must be documented in the participant's medical record. In any circumstance, every effort should be made to document participant outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the participant return for a final visit, if applicable, and follow up with the participant regarding any unresolved AEs.

If the participant withdraws from the study, and also withdraws consent 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.

8. ASSESSMENTS

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

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

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

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

Adherence to the study design requirements, including those specified in the schedule of activities, 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 the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of 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. Pregnancy Testing (Applicable to Stage 1 Participants Only)

For female participants of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of investigational product. A negative pregnancy test result is required before the participant may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). 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, the participant will be withdrawn from administration of investigational product and from the study.

In the case of a positive confirmed pregnancy *after* administration of investigational product, the participant may remain in the study for blood sample collections and safety monitoring.

8.2. 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 (participant's parent) may request that her samples (child's 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.

8.3. Immunogenicity

Pfizer will be responsible for all immunogenicity assays. 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. GBS Antibody Testing

Sera collected from nonpregnant women (Stage 1) and maternal participants (Stages 2 and 3) throughout the study and from infant participants will be assayed for GBS6 serotype-specific anticapsular antibodies. Sample collection, processing, storage, and shipping information can be found in the SRM or equivalent manual. OPA results for the 6 serotypes (Ia, Ib, II, III, IV, and V) will be determined in study participants' blood samples collected at prespecified time points. Results will be reported as OPA titers. Concentrations of anticapsular IgG for the 6 serotypes (Ia, Ib, II, III, IV, and V) will be determined in all participants for each blood sample by direct Luminex immunoassay (dLIA) and reported as IgG concentrations. CCI [redacted]

CCI [redacted]

8.3.3. Assessment of Antibody Responses to Routine Pediatric Vaccines in Infant Participants From South Africa (Stages 2 and 3)

Sera from the 18-week and 12-month blood draws in infant participants will be assayed for antibodies to CCI [redacted]

CCI [redacted]

8.5. Safety Parameters

Safety parameters will be assessed as described in the schedule of activities, Section 7, and below. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A medical history and physical examination will be performed on all nonpregnant women and maternal participants, to establish a baseline. Significant medical history and observations from the physical examination will be documented in the CRF.

The safety parameters include e-diary reports of local reactions and systemic events that occur in the 7 days after investigational product administration. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 8.5.2.

Acute reactions within the first 30 minutes after investigational product administration will be assessed and documented in the AE CRF.

In addition, AEs, MAEs, and SAEs are collected, recorded, and reported as defined in Section 9.

8.5.1. Participant Electronic Diary

The participant will be asked to monitor and record local reactions, systemic events, including fever, and antipyretics/pain medication used to prevent and/or treat symptoms, within a fixed time window each day for 7 days following vaccination (where Day 1 is the day of vaccination) on a system that uses a personal digital assistant (PDA) or other technology. In Stages 2 and 3, a baseline assessment (nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, or joint pain over the previous month) prior to vaccination will be recorded in the e-diary. 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 antipyretics/pain medication used to prevent and/or 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 (see Stopping Rules in Section 8.7).

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.

8.5.2. 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.[63]

8.5.2.1. Local Reactions

From Day 1 to Day 7, where Day 1 is the day of vaccination, participants will be asked to assess pain at the injection site, redness, and swelling 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 then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 4 below. 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 4 below. 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 can 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 4. 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
Erythema/ Redness	2.5 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 (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Induration/ Swelling	2.5 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 (≥21 measuring device units)	Necrosis

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

8.5.2.2. Systemic Events

In Stages 2 and 3, prior to vaccination, on Day 1, a baseline assessment (nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain over the previous month) will be recorded in the e-diary. From Day 1 to Day 7, where Day 1 is the day of vaccination, participants will be asked to assess nausea/vomiting, diarrhea, headache, fatigue/tiredness, 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 5 below. 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/tiredness, muscle pain, or joint pain) within 7 days after vaccination. Study staff may also contact the participant to obtain additional information on Grade 3 events entered into the e-diary.

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

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

Table 5. 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
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
Fatigue/Tiredness	No interference with activity	Some interference with activity	Significant; prevents daily activity[c]	Emergency room visit or hospitalization

Table 5. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

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

8.5.2.3. Fever

In order to record information on fever, a digital thermometer will be given to the participant with instructions on how to measure oral temperature at home. Temperature will be collected in the evening daily for 7 days following vaccination (where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature less than 38.0°C [100.4°F] in order to collect a stop date in the CRF). A participant with a fever >40.0°C (>104.0°F) 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 ≥39°C (≥102.1°F) is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 6 below:

Table 6. Ranges for Fever

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

If a fever 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.

8.5.3. Laboratory Tests

For Stage 2 sentinel-cohort participants, the safety laboratory tests in Table 7 will be performed at times defined in the schedule of activities and Section 7 of the protocol.

Table 7. Laboratory Tests

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

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

A toxicity grading scale adapted for use in pregnant women will be used to grade laboratory test abnormalities.[64] Please refer to the SRM for further details.

If abnormal laboratory parameters are reported at screening (Visit 0) or Visit 2 and the investigator believes the results to be erroneous, the abnormal laboratory parameters may be retested.

8.6. Use of Antipyretic/Pain Medication

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

8.7. Stopping Rules

Safety will be evaluated according to the stopping rules defined below. Stopping rules will be in effect and apply as detailed below to participants enrolled in sentinel cohorts (sentinel-cohort stopping rules 1 to 8) and participants enrolled in either sentinel or expanded cohorts (stopping rule 9) and will apply only to GBS6-vaccinated participants. "Dose level" refers to the group composed of participants receiving either formulation (with, and without $AlPO_4$) at the specified dose of polysaccharide. E-diary data confirmed to be entered by the participant in error will not contribute toward a stopping rule.

If it is suspected that a stopping rule has been met based on blinded safety assessment, the sponsor's designated unblinded personnel (and their backup designees) will seek to verify whether a stopping rule has been met based on unblinded randomization information. During this verification process, the investigational sites will be instructed by the sponsor not to administer any further investigational product. If the unblinded sponsor personnel determine that a stopping rule has not been met, then the sponsor will notify investigational sites that administration of the investigational product may continue according to the clinical trial protocol.

In the event that the unblinded sponsor personnel confirm that a stopping rule is met, enrollment and administration of the investigational product at that dose level will not continue until the IRC has reviewed all safety data and provided recommendations to the EDMC. The EDMC will review the safety data and IRC recommendations and agree or provide an alternate recommendation (to be detailed in the IRC and EDMC charters). Although enrollment and vaccination activities at that dose level will stop until IRC and EDMC review is complete and the issue is resolved, all other routine study conduct activities such as ongoing data entry, reporting of AEs, participant e-diary completion, participant follow-up including blood draws, etc., must continue during this time.

Although both formulations (with and without $AlPO_4$) at a given dose level will be evaluated for contribution to stopping rules together, it is possible that the recommendations may include halting or continuing enrollment with either or both formulations at a given dose level.

A stopping rule will be considered to have been met if any of the following occur in a sentinel cohort:

1. If any GBS6-vaccinated participant in a sentinel cohort develops an SAE within 30 days following vaccination for which there is no other clear attributable cause, or if the investigator determines that the SAE is related to vaccination.

2. If any GBS6-vaccinated participant in a sentinel cohort of a given dose level experiences a prompted local reaction or systemic event considered related to vaccination that results in an emergency room visit, or a local equivalent to this type of visit, or has local necrosis or exfoliative dermatitis (Grade 4 event) within 7 days following vaccination, or a Grade 4 laboratory abnormality at or before the 2-week postvaccination visit.

3. If ≥6 GBS6-vaccinated participants in a sentinel cohort of a given dose level (28 participants in total receive a GBS6 dose/sentinel cohort) experience the same Grade 3 local reaction or systemic event (see Table 4 and Table 5) within 7 days following vaccination, not attributable to any other cause, including:

    - Local redness
    - Local swelling
    - Local pain
    - Headache
    - Fatigue
    - Joint pain
    - Muscle pain
    - Nausea/vomiting
    - Diarrhea

4. If ≥2 GBS6-vaccinated participants in a sentinel cohort of a given dose level (28 participants in total receive a GBS6 dose/sentinel cohort) experience the same or similar Grade 3 unsolicited AE within 7 days following vaccination, or laboratory abnormality at or before the 2-week postvaccination visit, not attributable to any other cause.

5. If ≥2 GBS6-vaccinated participants in a sentinel cohort of a given dose level (28 participants in total receive a GBS6 dose/sentinel cohort) experience fever ≥39.0°C (≥102.1°F) for ≥2 consecutive days within 7 days following vaccination, for which there is no other clear attributable cause.

6. If any GBS6-vaccinated participant in the sentinel cohort of a given dose level (28 participants in total receive a GBS6 dose/sentinel cohort) experiences a confirmed fever >40.0°C (>104.0°F) for 1 daily measurement within 7 days following vaccination, for which there is no other clear attributable cause.

7. If ≥2 GBS6-vaccinated participants in a sentinel cohort of a given dose level (28 participants in total receive a GBS6 dose/sentinel cohort) experience premature labor or premature rupture of membranes within 14 days after vaccination.

8. If any GBS6-vaccinated participant in a sentinel cohort of a given dose level experiences severe vaginal bleeding (eg, partial abruption), severe preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, or life-threatening sequelae of preeclampsia (eg, pulmonary edema), stillbirth, or fetal loss within 14 days after vaccination. Refer to the SRM for further details.

In addition, a stopping rule will be considered to have been met if the following occurs in either a sentinel or an expanded cohort:

9. If any GBS6-vaccinated participant (in either a sentinel or an expanded cohort) develops an SAE during participation in the study following vaccination for which the investigator determines that the SAE is related to vaccination.

8.8. Other Safety Monitoring

8.8.1. Adverse Events

AEs and SAEs reported outside of the e-diary are recorded and reported as described in Section 9.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.5).

During the active collection period as described in Section 9.1.4, each participant/parent/legal guardian/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

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

8.8.2. Immediate Adverse Events

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.

8.8.3. Medically Attended Adverse Events

MAEs will be assessed from screening for all participants up to Visit 4 (Stage 1) for nonpregnant participants, up to Visit 9 for maternal participants (Stages 2 and 3), and up to Visit 7 for infant participants (Stages 2 and 3). In addition, for participants receiving the booster vaccination in Stage 1, MAEs will be assessed from Visit 5 to Visit 10.

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

8.8.4. Adverse Events of Special Interest

Developmental delay, major congenital disorders, and suspected or confirmed GBS disease in infant participants will be reported from delivery through the end of the study (12-month postdelivery visit).

8.8.5. Routine Medical Facility Visits and Elective Hospitalizations Not Associated With Adverse Events

Routine visits to medical facilities and elective hospitalizations not associated with an AE (ie, healthcare visits for preventive care, or for routine physical examinations) will not be collected.

9. ADVERSE EVENT REPORTING

For maternal-immunization clinical studies conducted in pregnant women, data on the exposure during pregnancy (EDP) as well as pregnancy outcome are collected and analyzed in the clinical database. For these studies, in general, EDP cases are not reportable unless associated with SAEs/nonserious AEs. For this study, this will be applicable to maternal participants enrolled into Stages 2 and 3.

The term "participant" in this section refers to (1) nonpregnant participants; (2) the maternal participant and her fetus; and after delivery (3) the maternal participant and (4) the infant participant.

9.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Vaccine Serious Adverse Event (SAE) Reporting 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 (for Stage 1 participants only), and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
Stage 1 participants		
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)
Stages 2 and 3 (maternal and infant participants)		
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study via occupational exposure	None	Occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of investigational product group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports.

In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section, Section 9.2.3). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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. Any pertinent additional information must be reported on the Vaccine SAE Reporting Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

The investigator must contact the Pfizer study physician directly as soon as possible after becoming aware of:

- A severe AE occurring within 7 days after vaccination in the sentinel cohort (Stage 2).
- An SAE occurring within 30 days after vaccination in the sentinel cohort (Stage 2).
- Premature labor or premature rupture of membranes within 14 days after vaccination in the sentinel cohorts (Stage 2).
- Severe vaginal bleeding (eg, partial abruption), severe preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, or life-threatening sequelae of preeclampsia (eg, pulmonary edema), stillbirth, or fetal loss within 14 days after vaccination, in the sentinel cohorts (Stage 2).
- An SAE occurring during the study following vaccination for which the investigator determines that the SAE is related to vaccination (Stage 2 sentinel or expanded cohort).

Additional information regarding such events and the reporting requirements can be found in the SRM or equivalent.

The investigator must contact the Pfizer study physician directly as soon as possible after becoming aware of an AE of special interest. This notification does not replace any of the standard AE reporting requirements as described above. Additional information is included in the SRM.

9.1.1. Additional Details on Recording Adverse Events on the CRF

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

9.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study participant/parent(s). In addition, each study participant/parent(s) will be questioned about the occurrence of AEs in a nonleading manner.

9.1.3. Withdrawal From the Study Due to Adverse Events (see also the Participant Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the Vaccine SAE Reporting Form, in accordance with the Requirements section, Section 9.1, above.

9.1.4. Time Period and Frequency for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each nonpregnant participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 3, and from Visit 5 to Visit 7. Between Visit 3 and Visit 4, and between Visit 7 and Visit 10, only SAEs (including hospitalizations) and MAEs will be reported.

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each maternal participant including her fetus begins from the time the maternal participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days (except as indicated below) after the last administration of the study intervention.

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

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

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

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

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

9.1.4.1. Stage 1

The investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through Visit 3. At Month 6 (Visit 4), the participant will be contacted by telephone to inquire about MAEs and SAEs, including hospitalizations since Visit 3. For participants receiving the booster vaccination, site staff will ensure the active elicitation and collection of AEs and SAEs from Visit 5 to Visit 7. At Visit 8 (3-month booster vaccination follow-up visit), Visit 9 (6-month booster vaccination follow-up visit), and Visit 10 (blood draw follow-up visit), MAEs and SAEs (including hospitalizations) since the previous visit will be recorded.

Immediate AEs will be reported as detailed in Section 8.8.2.

9.1.4.2. Stages 2 and 3 – Maternal Participants

In this study, the investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through Visit 3. At 1 week following delivery (Visit 5), the participant will be contacted by telephone to inquire about MAEs and SAEs, including hospitalizations, since Visit 3. At all subsequent visits (Visits 6, 7, 8, and 9), only MAEs and SAEs, including hospitalizations, will be reported.

Immediate AEs will be reported as detailed in Section 8.8.2.

In addition, AEs occurring up to 48 hours after the Visit 4, Visit 6, and Visit 9 blood draws that are related to study procedures must be reported in the CRF.

9.1.4.3. Stages 2 and 3 – Infant Participants

The investigator and site staff will ensure the active elicitation and collection of AEs and SAEs from birth (Visit 1) through Visit 3. At subsequent visits (Visit 4, Visit 5, Visit 6, and Visit 7), only AEs of special interest, MAEs, and SAEs, including hospitalizations, will be reported.

In addition, AEs occurring up to 48 hours after the Visit 4, 5, and 7 blood draws that are related to study procedures must be reported in the CRF. In addition, AEs occurring up to 48 hours after the Visit 4 CCI [redacted] that are related to study procedures must be reported in the CRF.

Refer to Table 8 for a summary of AE/SAE collection.

Table 8. Time Period for Collecting AE/SAE Information

Safety Event	Stage 1	Stages 2 and 3 Maternal Participant	Stages 2 and 3 Infant Participant
Nonserious AE	Consent – Visit 3 Visit 5 – Visit 7	Consent – Visit 3	Visit 1 (birth) – Visit 3
SAE	Consent – Visit 4 Visit 5 – Visit 10	Consent – Visit 9	Visit 1 – Visit 7
MAE	Consent – Visit 4 Visit 5 – Visit 10	Consent – Visit 9	Visit 1 – Visit 7
AE of special interest	N/A	N/A	Visit 1 – Visit 7
Immediate AE	Within 30 minutes of IP administration	Within 30 minutes of IP administration	N/A
AE related to study procedure	Not applicable[a]	Visit 4, Visit 6, and Visit 9 (up to 48 hours after blood draw)	Visit 4, Visit 5, and Visit 7 (up to 48 hours after blood draw/swab collection)

Abbreviations: IP = investigational product; MAE = medically attended adverse event; N/A = not applicable.

a. Study procedures will only be performed in Stage 1 during the standard AE/SAE reporting period, thus AEs related to study procedures are not applicable. Therefore, during Stage 1, these events will be reported as per standard AE reporting requirements detailed in Section 9.1.4.1.

9.1.4.4. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 9.1.4 are reported to Pfizer Safety on the Vaccine SAE Reporting Form, immediately upon awareness and under no circumstance should this exceed 24 hours, and the Exposure During Pregnancy Supplemental Form (Stage 1 participants only), if applicable. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, including miscarriage and missed abortion, intrauterine fetal demise, neonatal death [defined as those deaths that occur within 1 month of birth], or congenital anomaly [defined as structural or functional anomalies (eg, metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life]).[65] These SAEs can occur 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 and record this information in the CRF. In addition, infant deaths after 1 month of age should be reported as SAEs and recorded in the CRF.

Further follow-up may be requested by the sponsor and will be handled on a case-by-case basis (eg, follow-up on preterm infant participants to identify developmental delays).

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.

The same is applied for those SAEs after the active collection period has ended should they occur to the fetus. In addition, infant deaths that occur after 12 months of age should be reported as SAEs when the investigator believes the death has at least a reasonable possibility of being related to investigational product.

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.

9.1.4.5. Recording Nonserious AEs and SAEs on the CRF

All AEs/SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 9.1.4, will be recorded on the AE section of the CRF.

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

The investigator obtains general information on the pregnancy and its outcome for all study participants. The investigator will follow the pregnancy until completion (or until pregnancy termination). 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, including miscarriage and missed abortion, intrauterine fetal demise, neonatal death [defined as those deaths that occur within 1 month of birth], or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should record this information in the CRF. In addition, infant deaths after 1 month of age should be recorded in the CRF as SAEs.

9.1.5. Follow-up of AEs and SAEs

After the initial AE or 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 7.5.1).

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.

9.1.6. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. 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. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

9.1.7. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9.2. Definitions

9.2.1. Adverse Events

An AE is any untoward medical occurrence in a study participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- EDP (Stage 1 participants only);
- Exposure via breastfeeding (Stage 1 participants only);
- Vaccination error;
- Occupational exposure.

9.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

9.2.3. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

9.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, participant has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures, including vaginal delivery procedures and cesarean deliveries. These should be noted in the baseline documentation for the entire protocol and/or for the individual participant.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

9.3. Severity Assessment

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:	
MILD	Does not interfere with participants' usual function.
MODERATE	Interferes to some extent with participants' usual function.
SEVERE	Interferes significantly with participant's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the participant's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. A severity assessment will be collected on the AE CRF for all AEs.

9.4. Special Situations

9.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections and will be handled as SAEs in the safety database.

9.4.2. 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 for participants enrolled in Stage 1 or the expanded cohorts for Stage 2 and Stage 3. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin (T bili) elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a T bili 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 T bili 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 T bili above the normal range: T bili 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 T bili 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 T bili, 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, alkaline phosphatase, and acetaminophen drug and/or protein adduct levels. 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) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili 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.

9.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure (Stage 1 Only)

Exposure to the investigational product under study during pregnancy or breastfeeding (applicable only to Stage 1 participants) and occupational exposure (applicable to participants in all study stages) are reportable to Pfizer Safety within 24 hours of investigator awareness. Refer to Section 9.1 for further details.

9.4.3.1. Exposure During Pregnancy

EDP should be reported for all participants in Stage 1 and for all women in Stages 2 and 3 after delivery and before the end of the study (Visit 9).

For both unapproved/unlicensed products and for marketed products, an 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 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 Vaccine SAE Reporting 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 infant participants 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.

9.4.3.2. Exposure During Breastfeeding

Exposure during breastfeeding reports are not expected for maternal participants who breastfeed a child delivered during the study.

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 Vaccine SAE Reporting 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 participant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

9.4.3.3. 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 Vaccine SAE Reporting 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 Vaccine SAE Reporting Form is maintained in the investigator site file.

9.4.4. Vaccination Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as vaccination errors.

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

9.4.4.1. Vaccination Errors

Vaccination 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.

Vaccination errors include:

- Vaccination errors involving participant exposure to the investigational product;
- Potential vaccination errors or uses outside of what is foreseen in the protocol that do or do not involve the participating 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 vaccination errors occurring to a study participant are to be captured on the vaccination error page of the CRF, which is a specific version of the AE page.

In the event of a vaccination dosing error, the sponsor should be notified immediately.

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

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

10. DATA ANALYSIS/STATISTICAL METHODS

Methodology for summary and statistical analyses of the data collected in this study is described here and additional details will be documented in the 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.

All analyses for both immunogenicity and safety data will be descriptive in nature.

10.1. Sample Size Determination

This is a Phase 1/2 randomized, placebo-controlled, observer-blinded study to assess safety, tolerability, and immunogenicity of GBS6 in healthy nonpregnant as well as pregnant women and their infant participants. The study consists of 3 stages. The sample sizes at each stage are not driven by any specific hypothesis testing.

Approximately 66 nonpregnant women will be enrolled at Stage 1, 22 participants per group to receive placebo (saline control) or GBS6 (20 µg CPS/serotype/dose) with or without $AlPO_4$. Participants in Stage 1 will also receive a booster dose of GBS6 (20 µg CPS/serotype/dose with $AlPO_4$) approximately 2 years after the initial dose of investigational product. Sample size for the participants receiving GBS6 booster dose is dependent upon the number of participants providing consent to continue in the study.

Approximately 360 pregnant women will be enrolled at Stage 2, 40 participants at each GBS6 dose/formulation and a total of 120 participants in the placebo group. Refer to Table 2 for a detailed description of the number of participants per group. Approximately 216 pregnant women will be enrolled at Stage 3 (approximately 162 from South Africa/UK and 54 from the US), 108 participants at the selected GBS6 dose/formulation and 108 participants in the placebo group. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks.

Table 9 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 14 participants in each dose/formulation group, there is 77% probability of observing at least 1 AE.

Table 9. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Sample Size (N)	Assumed True Event Rate of an AE					
	1.0%	2.0%	2.5%	3.0%	5.0%	10.0%
14	0.13	0.25	0.30	0.35	0.51	0.77
22	0.20	0.36	0.43	0.49	0.68	0.90
28	0.25	0.43	0.51	0.57	0.76	0.95
40	0.33	0.55	0.64	0.70	0.87	0.99
44	0.36	0.59	0.67	0.74	0.90	0.99
80	0.55	0.80	0.87	0.91	0.98	>0.99
120	0.70	0.91	0.95	0.97	>0.99	>0.99
240	0.91	0.99	>0.99	>0.99	>0.99	>0.99
348	0.97	>0.99	>0.99	>0.99	>0.99	>0.99

Abbreviations: $AlPO_4$ = aluminum phosphate; CPS = capsular polysaccharide.
Note: In Stage 1, 44 nonpregnant women are planned to be vaccinated with GBS6 (20 µg CPS/serotype/dose) with or without $AlPO_4$ (22/formulation). In each sentinel cohort of Stage 2, 28 maternal participants are planned to be vaccinated with each dose of GBS6 with or without $AlPO_4$ (14/formulation). In Stage 2, a total of 80 maternal participants are planned to be vaccinated with each dose of GBS6 with or without $AlPO_4$ (40/formulation), and a total of 240 maternal participants are to be vaccinated with any dose of GBS6 with or without $AlPO_4$ (120/formulation). In the entire study, 348 maternal participants are to be vaccinated with any dose of GBS6.

10.2. Immunogenicity Analysis

Immunogenicity data will be analyzed separately for nonpregnant women (Stage 1), maternal participants (Stages 2 and 3), and their infant participants (Stages 2 and 3).

10.2.1. Immunogenicity Analysis Populations

For the immunogenicity analyses, 2 analysis populations will be defined separately for nonpregnant women, maternal participants, and their infant participants: evaluable immunogenicity and modified intent to treat (mITT) populations.

For the immunogenicity analyses, nonpregnant and maternal participants will be analyzed according to the investigational product received for the evaluable immunogenicity population and the investigational product as randomized for the mITT population. Infant participants will be analyzed according to the investigational product received by their mothers (maternal participants) for the evaluable immunogenicity population and the investigational product assigned to their mothers (maternal participants) for the mITT population. The evaluable immunogenicity population is considered to be the primary population for the immunogenicity analyses.

10.2.1.1. Nonpregnant Women (Stage 1)

To be included in the evaluable immunogenicity population of primary vaccination, in general, a Stage 1 participant must have been eligible for the study, have received GBS6 or placebo as randomized, have had blood drawn within the specified time frames, have had at least 1 valid and determinate assay result for the proposed analysis, and have had no other major protocol violations. To be included in the mITT population, a Stage 1 participant must be randomized and have had at least 1 valid and determinate assay result related to the proposed analysis.

To be included in the evaluable immunogenicity population of booster vaccination, in general, a Stage 1 participant must have been eligible for the study, have received a booster dose of GBS6, have had blood drawn within the specified time frames, have had at least 1 valid and determinate assay result for the proposed analysis, and have had no other major protocol violations. To be included in the mITT population, a Stage 1 participant must have at least 1 valid and determinate assay result related to the proposed analysis.

10.2.1.2. Maternal Participants (Stages 2 and 3)

Similarly, to be included in the evaluable immunogenicity population, a maternal participant from Stage 2 or 3 must have been eligible for the study, have received GBS6 or placebo as randomized, have had blood drawn within the specified time frames, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations. To be included in the mITT population, a maternal participant from Stage 2 or 3 must be randomized and have at least 1 valid and determinate assay result related to the proposed analysis.

10.2.1.3. Infant Participants (Stages 2 and 3)

To be included in the evaluable immunogenicity population, an infant participant from Stage 2 or 3 must have been eligible for the study, the infant participant's mother must have received GBS6 or placebo as randomized, and the infant participant must have had blood drawn within the specified time frames, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations. To be included in the mITT population, the infant participant's mother must be randomized, and the infant participant must have at least 1 valid and determinate assay result related to the proposed analysis.

10.2.2. Analysis of Immunogenicity Endpoints

Immunogenicity endpoints are secondary or exploratory in the study as listed in Section 3.2 and Section 3.3. Descriptive summary statistics will be provided for all immunogenicity endpoints. No formal between-group comparison will be made.

Descriptive evaluations include GBS6 serotype-specific IgG GMCs and OPA GMTs measured at prespecified time points and will be summarized by vaccine group.

GBS6 serotype-specific IgG concentrations will be logarithmically transformed for analysis. For each serotype, GMCs will be calculated at all blood draw visits. Two (2)-sided 95% confidence intervals (CIs) for the GMCs will be constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using Student's t distribution.

OPA GMTs and the corresponding 2-sided 95% CIs for the GBS6 serotype-specific OPA titers will be computed using similar methods to those for IgG concentrations.

The proportions of participants achieving defined GBS6 serotype-specific IgG concentrations and OPA titers will be summarized descriptively at prespecified time points as counts and percentages with 2-sided 95% exact CIs by vaccine group.

All of the binary endpoints will be descriptively summarized with 2-sided exact 95% CIs using the Clopper-Pearson method.

Reverse cumulative distribution curves (RCDCs) for combination of prespecified time points and vaccine groups will be generated for each GBS6 serotype. Additionally, antibody response line plot of geometric means and the associated 95% CIs will be presented at each analysis time point by vaccine group and serotype.

Detailed analyses of all the immunogenicity endpoints including additional exploratory analyses and graphical displays will be described in the SAP.

10.3. Safety Analysis

Safety data will be analyzed separately for nonpregnant women (Stage 1), maternal participants (Stages 2 and 3), and their infant participants (Stages 2 and 3).

10.3.1. Safety Population

A safety population will be defined separately for nonpregnant women, maternal participants, and their infant participants.

For the safety analyses, nonpregnant and maternal participants will be analyzed according to the investigational product received and infant participants will be analyzed according to the investigational product their mothers (maternal participants) received.

10.3.1.1. Nonpregnant Women (Stage 1)

All Stage 1 participants receiving a primary dose of GBS6 or placebo will be included in the safety population of primary vaccination.

All Stage 1 participants receiving a booster dose of GBS6 will be included in the booster safety population.

10.3.1.2. Maternal Participants (Stages 2 and 3)

All maternal participants from Stages 2 or 3 receiving a dose of GBS6 or placebo will be included in the safety population.

10.3.1.3. Infant Participants (Stages 2 and 3)

All infant participants who are enrolled in the study will be included in the safety population.

10.3.2. Analysis of Safety Endpoints

The safety endpoints as listed in Section 3.1 are primary in the study and their analyses are based on the safety population.

The safety analyses for Stage 1 nonpregnant women and maternal participants from Stages 2 and 3 are descriptive evaluations of local reactions, systemic events, AEs, MAEs, and SAEs by vaccine group. In addition, clinical laboratory abnormalities, delivery outcomes, and obstetric complications for maternal participants from Stages 2 and 3 will be summarized by vaccine group. The safety analyses for infant participants from Stages 2 and 3 are descriptive evaluations of birth outcomes, AEs, MAEs, AEs of special interest, and SAEs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).

Descriptive summary statistics for continuous outcomes will include number of participants, mean, standard deviation, median, minimum, and maximum and 2-sided 95% CIs for the mean, as needed. For categorical outcomes, number and percentage of participants in each category and 2-sided 95% exact CIs using Clopper-Pearson method will be provided.

10.4. Analysis Timing

In addition to the planned safety data review while the study is ongoing, 4 interim analyses are planned for this study.

The first interim analysis will be performed when 1-month postvaccination safety data from all participants enrolled in Stage 1 are available. Stage 2 of the study will be initiated based on results from the first interim analysis as well as those from the 1-month postvaccination safety and immunogenicity data of 3 different dose levels of GBS6 formulated with or without $AlPO_4$ from the prior US FIH Phase 1/2 study (C1091001). Both the IRC and EDMC will review all the available unblinded data and the IRC in consultation with the EDMC will make recommendations regarding the study proceeding to Stage 2. For details of sponsor blinding, refer to Section 6.8.

The second interim analysis will be performed when delivery/birth safety and immunogenicity data from all maternal participants in the sentinel cohorts and their infant participants in Stage 2 are available. Safety and immunogenicity data from all maternal sentinel-cohort study participants and their infants will be included in the analysis. The second interim analysis is being conducted for internal planning purposes only. These unblinded data will be reviewed by the IRC. For details of sponsor blinding, refer to Section 6.8.

The third interim analysis will be performed when delivery/birth safety and immunogenicity data from all maternal participants and their infant participants in Stage 2 are available. All available safety and immunogenicity data from all study participants will be included in the analysis. The primary objective of the third interim analysis is to select a dose and formulation for Stage 3. These unblinded data will be reviewed by the IRC.

The final GBS6 dose and formulation to take into Stage 3 and further development will be selected after this review. For details of sponsor blinding, refer to Section 6.8.

The fourth interim analysis will be performed when delivery/birth safety and immunogenicity data from all maternal participants and their infant participants in Stage 3 are available. All available safety and immunogenicity data from all study participants will be included in the analysis. The primary objective of the fourth interim analysis is to support internal development decisions and potential regulatory agency interactions for the program. These unblinded data will be reviewed by the IRC. For details of sponsor blinding, refer to Section 6.8.

No multiplicity adjustments will be applied for these assessments.

After the completion of the 12-month postdelivery/birth follow-up visit for participants in Stage 3, a clinical study report (CSR) including all unblinded safety and immunogenicity data gathered from all participants from each of the 3 stages will be issued. Safety and immunogenicity data from maternal and infant participants in Stages 2 and 3 will be analyzed separately.

Safety and immunogenicity data from infant participants who are born to maternal participants receiving the same vaccine dose/formulation or placebo in Stages 2 and 3 will be analyzed separately.

Immunogenicity data from Stage 3 will also be analyzed separately by country (US/UK, South Africa).

10.5. Data Monitoring Committee

This study will use both an IRC and an EDMC.

The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter, as well as the analysis results with the safety data cutoff at 1 month after vaccination for participants from Stage 1 as described in Section 10.4 above. The EDMC will also meet for an ad hoc safety review should enrollment of Stage 2 participants be halted, to review the IRC recommendation and make a recommendation before enrollment may be restarted, the protocol modified, or enrollment terminated.

The recommendations made by the EDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

The EDMC will not participate in the Stage 2 dose-escalation processes but will participate in the stopping rule and overall safety data review processes, in line with the remit of the EDMC charter.

11. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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.

12. DATA HANDLING AND RECORD KEEPING

12.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included participant. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required.

The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

12.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating participants (sufficient information to link records, eg, CRFs and hospital records), all original signed ICDs, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

13. ETHICS

13.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICDs, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the participants. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

13.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), the ICH Guideline for GCP, and the Declaration of Helsinki.

13.3. Participant Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. Such measures will include omitting participant names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The 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, when study data are compiled for transfer to Pfizer and other authorized parties, participant names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, participant-specific code. The investigator 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, Pfizer will maintain high standards of confidentiality and protection of participants' personal data consistent with the CSA and applicable privacy laws. The ICDs and any participant recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The ICDs used during the informed consent process and any participant recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study participant, or parent(s) if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The investigator further must ensure that each study participant, or parent(s) if a minor, 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.

Whenever consent is obtained from a participant's parent(s), the participant's assent (affirmative agreement) must subsequently be obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his or her own consent, the source documents must record why the participant did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the participant's legally acceptable representative, the consent signer's relationship to the study participant (eg, parent, spouse), and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each participant before any study-specific activity is performed. The investigator will retain the original of each participant's signed consent.

Before any study-specific activity is performed, the investigator, or a person designated by the investigator, will obtain written informed consent from each maternal participant. This will include written informed consent for the mother and the fetus during the pregnancy and the infant participant's continuation in the study after delivery. Informed consent will be obtained from the father of the fetus/infant participant if mandated by local requirements.

13.4. 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.

14. DEFINITION OF END OF TRIAL

14.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as the last visit of the last participant.

15. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of GBS6 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating participants and the hospital pharmacy (if applicable) within 30 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

16. PUBLICATION OF STUDY RESULTS

16.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial 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 SOPs.

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

16.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study participants, and the CSA will control as to all other issues.

17. PROTOCOL AMENDMENT HISTORY

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

Amendment 7 (20 Oct 2022)

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1: Protocol Summary Section 1.2: Schedule of Activities Section 2.2.5: Study Rationale Section 3.3.2: Exploratory Objectives: Stages 2 and 3 Section 3.3.6: Exploratory Endpoints (Infant Participants): Stages 2 and 3 Section 7.3.5: Visit 5 – 18-Week Postdelivery Follow-Up (119-133 Days After Delivery) Section 7.3.7: Visit 7 – 12-Month Postdelivery Follow-Up (365-385 Days After Delivery) Section 8.3.3: Assessment of Antibody Responses to Routine Pediatric Vaccines in Infant Participants From South Africa (Stages 2 and 3)	• Revised the infant blood draw schedule for the US and UK Stage 3 participants	• The pediatric immunization schedules in the US and UK differ with respect to administration of diphtheria and 13-valent pneumococcal conjugate vaccine. The revised infant blood schedule has changed to be in line with this pediatric immunization schedule.	• Substantial
Section 1: Protocol Summary Section 2.2.5: Study Rationale Section 4.1: Diversity of Study Population Section 4.4: Stage 3 Section 4.7: Number of Participants Section 4.7.3: Stage 3 Section 10.1: Sample Size Determination	• Amended US participant number from 200 to 36	• The adjusted proposed number of participants will be sufficient to evaluate and compare the GBS6 placental antibody transfer efficiency between maternal/infant pairs in the US and South Africa.	• Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 5.5: Exclusion Criteria – Stages 2 and 3 – Maternal Participants	• Amended exclusion criterion 8 to use BMI of ≥40 kg/m^2 from prepregnancy. If prepregnancy BMI is not available, the BMI at the time of the first obstetric visit during the current pregnancy may be used.	• This clarification was added to ensure enrollment of healthy pregnant women who are at no increased risk of pregnancy complications and will facilitate recruitment of suitable maternal participants for the study. Incorporated the Protocol Administrative Change Letter from September 2022.	• Nonsubstantial
Section 5.5: Exclusion Criteria – Stages 2 and 3 – Maternal Participants Section 6.10.2.2: Stages 2 and 3 – Maternal Participants	• Clarified exclusion criterion 15 regarding participants' receipt of licensed Tdap vaccinations	• This change has been made to improve clarity and provide guidance to investigational sites. Incorporated the Protocol Administrative Change Letter from September 2022.	• Nonsubstantial

Amendment 6 (26 Apr 2022)

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Background and Rationale Section 4.1: Diversity of Study Population Section 4.4: Stage 3 Section 4.7: Number of Participants Section 4.7.3: Stage 3 Table 1: Enrollment and Dose Escalation Design	• Added 200 maternal participants to be enrolled from the US into Stage 3.	• Data from additional participants will contribute to the safety database of maternal participants to support the initiation of the Phase 3 program. • Data will enable a better evaluation and comparison of GBS6 placental antibody transfer efficiency between maternal/infant pairs in the US and South Africa.

Section # and Name	Description of Change	Brief Rationale
Section 3.2.5: Secondary Endpoints: Stage 1 Section 3.2.6: Secondary Endpoints (Maternal Participants): Stages 2 and 3 Section 3.3.4: Exploratory Endpoints: Stage 1 Section 3.3.5: Exploratory Endpoints (Maternal Participants): Stages 2 and 3 Section 3.3.6: Exploratory Endpoints (Infant Participants): Stages 2 and 3 Section 8.3.1: GBS Antibody Testing	• Removal of OPA analysis as an exploratory endpoint for Stage 1 nonpregnant women, and Stage 2 and Stage 3 maternal and infant participants. • Removal of OPA analysis as a secondary endpoint for Stage 1 nonpregnant women.	• Data from the second and third interim analyses demonstrated robust immune responses, as measured by serotype-specific IgG and functional antibody response for serotype-specific OPA after GBS6 vaccination. These data support the use of anti-GBS capsular IgG levels to evaluate GBS6 vaccine protection against invasive GBS disease. However, the lower limits of quantitation (LLOQs) for serotype-specific OPAs were high, indicating that the OPA assays are not sensitive enough compared to IgG, and thus rendering the OPA assay unsuitable for measuring vaccine protection.
Section 1.1: Stage 3 Section 4.4: Stage 3	• Updated the fourth interim analysis that will be performed when all Stage 3 maternal participants and their infants have completed the delivery/birth visit and a protective threshold, once identified, will be based on infant IgG at birth.	• This change was implemented in protocol amendment 4, but these sections were missed in error.
Section 1.1: Statistical Methods Section 10.2: Immunogenicity Analysis Section 10.4: Analysis Timing	• Safety and immunogenicity data from maternal and infant participants from Stage 2 and 3 will be analyzed separately.	• This will enable separate analysis of maternal and infant participants in Stage 2 and Stage 3.
Section 1.2: Schedule of Activities Section 7.1.11: Visit 10 – Blood Draw Follow-up Visit (14-184 Days After Visit 9)	• Updated reference to the ICD for booster participants.	• Addition of ICD requirements that were missed at protocol amendment 5 for consistency across the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 5.10: Screen Failures	• Addition of the section to include specifics for screen failures.	• Section has been added to clarify the protocol.
Section 7.2.1: Visit 0 – Screening (Days -14 to -2 Prior to Vaccination)	• Updated wording to clarify the reason for ultrasound at screening.	• Additional information added for protocol clarification.
Section 10.4: Analysis Timing	• Immunogenicity data from Stage 3 will also be analyzed separately by country. (US/UK, South Africa).	• Separate analysis by country will allow the analysis of transplacental transfer ratios between US and South African mother-infant pairs.
Title Page	• Update of the ClinicalTrials.gov ID from NCT01193920 to NCT03765073.	• The ClinicalTrials.gov ID NCT01193920 is not applicable to this GBS6 study; the ID has been corrected to NCT03765073.

Amendment 5 (03 Nov 2021)

Section # and Name	Description of Change	Brief Rationale
Protocol Summary Section 1.2: Schedule of Activities Section 3.1.2: Primary Endpoints: Stage 1 Section 4.1: Stage 1 Section 4.5: Duration of Participant Participation Section 7.1.11: Visit 10 – Blood Draw Follow-up Visit (14-184 Days After Visit 9) Section 9.1.4.1: Stage 1 Section 9.1.4.3: Stages 2 and 3 – Infant Participants	• Added an additional blood draw visit for Stage 1 cohort booster participants.	• The additional blood draw visit for the Stage 1 cohort booster will provide additional serum to support the development of a universal reference standard assay, which is needed to inform a potential surrogate of protection for GBS6.
Title Page	• Added the EudraCT Number.	• Addition of the EudraCT Number because of the addition of a UK site for Stage 3. Incorporating the Protocol Administrative

Section # and Name	Description of Change	Brief Rationale
		Change Letter from August 2021.
Section 5: Study Population Section 5.1: Inclusion Criteria – Stage 1 Section 5.2: Inclusion Criteria – Stage 1 Booster Vaccination Section 5.3: Exclusion Criteria – Stage 1 Section 5.4: Inclusion Criteria – Stages 2 and 3 – Maternal Participants Section 5.5: Exclusion Criteria – Stages 2 and 3 – Maternal Participants Section 5.6: Inclusion Criteria – Infant Participants – Stages 2 and 3 Section 5.7: Exclusion Criteria – Infant Participants – Stages 2 and 3 Section 6.5: Investigational Product Storage Section 6.6: Investigational Product Accountability Section 6.6.1: Destruction of Investigational Product Supplies Section 7.5.1: Withdrawal of Consent Section 8: Assessments Section 8.5: Safety Parameters Section 8.8.1: Adverse Events Section 9.1.4: Time Period and Frequency for Collecting AE/SAE Information Section 9.1.4.4: Reporting SAEs to Pfizer Safety Section 9.1.4.5: Recording Nonserious AEs and SAEs on the CRF Section 9.1.5: Follow-up of AEs and SAEs Section 17: Protocol Amendment History	• Updated wording to match the new protocol template.	• Protocol template changes.

Amendment 4 (25 Nov 2020)

Section # and Name	Description of Change	Brief Rationale
Section 1: Introduction Section 2: Study Objectives and Endpoints Section 3: Study Design Section 4: Participant Eligibility Criteria Section 5: Investigational Products Section 6: Study Procedures Section 7: Assessments Section 8: Adverse Event Reporting Section 9: Data Analysis/Statistical Methods	• Added background information on clinical experience with repeated dosing • Added that Stage 1 participants (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 • Updated the objectives and associated analyses to be performed for Stage 1 participants (nonpregnant women) returning for the booster vaccination • Updated the eligibility and temporary delay criteria for Stage 1 participants (nonpregnant women) returning for the booster vaccination • Updated the Investigational Products section to include details of the booster vaccination, nonstudy vaccinations, and concomitant medications for Stage 1 participants (nonpregnant women) returning for the booster vaccination • Updated the safety monitoring and adverse event (AE) reporting procedures for Stage 1 participants (nonpregnant women) returning for the booster vaccination • Updated "Clinical Trial (CT) Serious Adverse Event (SAE) Report Form" to "Vaccine SAE Reporting Form" throughout Section 9 • Updated the fourth interim analysis that will be performed when all Stage 3 maternal participants and their infants have completed the delivery/birth visit and as a protective threshold	• Added that Stage 1 participants (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 and provide additional serum to support the development of a universal reference standard assay, which is needed to inform a potential surrogate of protection for the GBS6 vaccine • Updated the fourth interim analysis that will be performed when all Stage 3 maternal participants and their infants have completed the delivery/birth visit and as a protective threshold, once identified, will be based on infant IgG at birth. The interim analysis is being modified to be in line with this strategy.

Amendment 3 (27 May 2020)

Section # and Name	Description of Change	Brief Rationale
Section 2: Study Objectives and Endpoints Section 3: Study Design Section 4: Participant Eligibility Criteria Section 6: Study Procedures Section 7: Assessments Section 9: Data Analysis/Statistical Methods	• The gestational age of vaccination for participants in Stage 3 has been changed from ≥27 0/7 to ≤35 6/7 weeks' gestation to ≥24 0/7 to ≤35 6/7 weeks' gestation • The third interim analysis has been updated and will be performed when all Stage 2 maternal participants and their infants have completed the delivery/birth visit. • Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks • Text was added to Section 6.2 and Section 6.3 and the schedule of activities (Stages 2 and 3) to clarify that study visits can be conducted by telephone in the event of a disease outbreak or pandemic • The text in Section 6.3.1 and the schedule of activities was updated	• The gestational age of vaccination for participants in Stage 3 has been changed from ≥27 0/7 to ≤35 6/7 weeks' gestation to ≥24 0/7 to ≤35 6/7 weeks' gestation, to enable evaluation of safety and immunogenicity at earlier gestational ages (second trimester) • The third interim analysis has been updated and will be performed when all Stage 2 maternal participants and their infants have completed the delivery/birth visit, as a protective threshold, once identified, will be based on infant IgG at birth. The interim analysis is being modified to be in line with this strategy

Section # and Name	Description of Change	Brief Rationale
Section 15: Publication of Study Results	to allow sites to calculate and record the Ballard score up to 72 hours after delivery. This will allow information to be obtained if unavailable at delivery. Incorporated the Protocol Administrative Change Letter from November 2019 • Added editorial changes in Section 7 and Section 15.1 to improve clarity	• Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks, to enable expanded evaluation of safety and immunogenicity data at the selected dose, in the second and third trimester of pregnancy • Text was added to Section 6.2 and Section 6.3 and the schedule of activities (Stages 2 and 3) to clarify that study visits can be conducted by telephone in the event of a disease outbreak or pandemic. This will allow for appropriate safety follow-up per protocol requirements. Incorporated the Protocol Administrative Change Letter from March 2020

Amendment 2 (18 Sep 2019)

Section # and Name	Description of Change	Brief Rationale
Section 6: Study Procedures Section 7: Assessments Section 8: Adverse Event Reporting	• Updated the text in Section 6.2.6 and the schedule of activities to allow sites CCI [redacted] • Updated the study procedures section for infant participants (Section 6.3) to include additional body systems to be evaluated for the physical examination, per regulatory feedback • Updated Section 6.3.1 to allow for the collection of delivery visit information from available sources • Updated the time window for the daily diary collection (Section 7.5.1 and the schedule of activities), since the time window opens in the afternoon (not the evening) • Updated text in the schedule of activities, Section 8.1.4.2, and Table 8 to clarify that adverse events (AEs) related to study procedures occurring up to 48 hours after the blood draw at Visit 4 should also be reported in the case report form (CRF)	• Updated the text in Section 6.2.6 and the schedule of activities to allow sites to CCI [redacted] Incorporated the Protocol Administrative Change Letter from July 2019 • Updated the study procedures section for infant participants (Section 6.3) to include additional body systems to be evaluated for the physical examination, per regulatory feedback. Incorporated the Protocol Administrative Change Letter from April 2019 • Updated Section 6.3.1 to allow for the collection of delivery visit information from available sources. Incorporated the Protocol Administrative Change Letter from August 2019 • Updated the time window for the daily diary collection (Section 7.5.1 and the schedule of activities) since the time window opens in the afternoon (not the evening). Incorporated the Protocol Administrative Change Letter from April 2019 • Updated text in the schedule of activities, Section 8.1.4.2, and Table 8 to clarify that adverse events (AEs) related to study procedures occurring up to 48 hours after the blood draw at Visit 4 should also be reported in the case report

Section # and Name	Description of Change	Brief Rationale
		form (CRF). Incorporated the Protocol Administrative Change Letter from July 2019

Amendment 1 (04 Feb 2019)

Section # and Name	Description of change	Brief Rationale
Section 2: Study Objectives and Endpoints Section 3: Study Design Section 5: Investigational Products Section 6: Study Procedures	• Added editorial changes throughout the document to improve clarity and to fix typographical errors • Provided clarification on the timing of internal review committee (IRC) reviews in the Protocol Summary and Section 3.2 • Updated the exploratory objective (Section 2.3.2) to be in line with the expected duration of coverage against invasive GBS disease in infants, which is 3 months • Made changes regarding the collection of concomitant medications to the schedule of activities and the Procedures section to ensure consistency with Section 5.10.3 • Made changes to the schedule of activities and the Procedures section for maternal participants to only measure height at the screening visit	• Updated the exploratory objective (Section 2.3.2) to be in line with the expected duration of coverage against invasive GBS disease in infants, which is 3 months. The 12-month time point has been removed as it is expected that passively acquired maternal antibodies will no longer be detectable. Applicable endpoints for this objective were removed in Section 2.3.6 • Made changes to the schedule of activities and the Procedures section for maternal participants to only measure height at the screening visit, since height is not expected to change significantly during the study • Added a statement confirming the rationale for the collection of date of

Section # and Name	Description of change	Brief Rationale
Section 9: Data Analysis/Statistical Methods	• Updated all temperature references to °C (°F) per local practice • Added a statement confirming the rationale for the collection of date of birth to the Procedures section (Section 6) • Updated Section 6.5.1 to accommodate local requirements for participants who are lost to follow-up	birth to the Procedures section (Section 6) • Updated Sections 5.8 and 9.4 to include an additional interim analysis that was added for internal planning purposes

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Appendix 1. Abbreviations

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

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
$AlPO_4$	aluminum phosphate
ALT	alanine aminotransferase
Apgar	appearance, pulse, grimace, activity, and respiration
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
CK	creatine kinase
CPS	capsular polysaccharide
CRF	case report form
CRM_{197}	cross-reactive material 197
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
dLIA	direct Luminex immunoassay
EC	ethics committee
EDD	estimated delivery date
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOD	early-onset disease
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration (United States)
FIH	first-in-human
FSH	follicle-stimulating hormone
GA	gestational age
GBS	group B streptococcus
GBS6	group B streptococcus 6-valent polysaccharide conjugate vaccine
GBS III-TT	group B streptococcus type III capsular polysaccharide-tetanus toxoid conjugate vaccine
GCP	Good Clinical Practice

Abbreviation	Term
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IAP	intrapartum antibiotic prophylaxis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IgG	immunoglobulin G
CCI [redacted]	
IND	investigational new drug application
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive Web-based response
LFT	liver function test
LMIC	low- and middle-income country
LMP	last menstrual period
LOD	late-onset disease
MAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
CCI [redacted]	
OPA	opsonophagocytic activity
PDA	personal digital assistant
PI	principal investigator
PT	prothrombin time
RBC	red blood cell
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure

Abbreviation	Term
SRM	study reference manual
SRSD	single reference safety document
T bili	total bilirubin
Tdap	tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine
UK	United Kingdom
ULN	upper limit of normal
US	United States
WBC	white blood cell

Document Approval Record

Document Name:	C1091002 Protocol Amendment 8 Clean Copy, 27 March 2023
Document Title:	A PHASE 1/2, RANDOMIZED, PLACEBO CONTROLLED, OBSERVER BLINDED TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MULTIVALENT GROUP B STREPTOCOCCUS VACCINE IN HEALTHY NONPREGNANT WOMEN AND PREGNANT WOMEN 18 TO 40 YEARS OF AGE AND THEIR INFANTS

Signed By:	Date(GMT)	Signing Capacity
PPD	27-Mar-2023 20:31:14	Business Line Approver
	28-Mar-2023 00:52:52	Final Approval