Protocol C1091002

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

Statistical Analysis Plan Amendment 4

Version: 5.0

Date: 02 Feb 2023

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) Amendment 4 for Study C1091002 is based on Protocol Amendment 7 dated 21 October 2022.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1.0	Not applicable	Not applicable
Amendment 1 2.0	• Added editorial changes throughout the document to improve clarity • Updated Section 3.4.3 to revise the feeding modality • Updated Section 3.6.1 to include the infant participants from Stages 2 and 3 • Updated Section 5.3.1 to include lower limit of quantitation (LLOQ) values for opsonophagocytic activity (OPA) • Updated Section 6.1.3.1 to revise the birth outcomes that will be summarized • Updated Section 7.2 to include an additional interim analysis for Stage 2 sentinel-cohort maternal participants and their infants	Based on Protocol Amendment 1 and team discussions
Amendment 2 3.0	• Updated Section 2.1.1.1 to add the booster dose primary objective of Stage 1 • Updated Section 2.1.2.1 to add the booster dose secondary objective of Stage 1 • Updated Section 2.2 study design to add the booster dose and the revised gestational age in Stage 3 • Updated Table 2 to add Stage 1 booster dose and adjusted notes accordingly • Updated Section 3.1.1 to add the booster dose primary endpoints of Stage 1 • Updated Section 3.2.1 to add the booster dose secondary endpoints of Stage 1 • Updated Section 3.3.1 to clarify the CCI [redacted] • Updated Section 3.4 baseline definition • Updated Section 3.6.1 to add booster dose adverse events (AEs) • Updated Table 8 to incorporate corrections for grading laboratory test abnormalities	Based on Protocol Amendment 4

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
	• Updated Section 3.6.4.1 to add booster dose physical examinations and vital signs • Updated Section 3.7.2.1 to add booster dose nonstudy vaccination and concomitant treatments • Updated Section 4.1.1 to add per protocol analysis set for Stage 1 booster dose • Updated Section 4.3.1 to add safety analysis set for Stage 1 booster dose • Updated Section 6.1.1 to add analyses of primary endpoints of booster dose in Stage 1 • Updated Section 6.2.1 to add analyses of secondary endpoints of booster dose in Stage 1 • Updated Section 6.3.2 to clarify the analyses of [redacted] • Updated Section 6.6.1 to add baseline summaries for booster dose in Stage 1 • Updated Section 6.7.1 to add AEs, MAEs, and SAEs of booster dose in Stage 1 • Updated Section 6.7.4 to add booster dose in Stage 1 • Updated Section 7 to add the modified interim analysis timings • Updated Section 9 to add booster dose endpoints	
Amendment 3 4.0	• Added editorial changes throughout the document to improve clarity • Updated Sections 2.1.1.2 and 2.1.3.1 to be aligned with the protocol • Updated Section 2.2.3 and Table 2 to specify that 200 more maternal participants will be enrolled in Stage 3 • Updated Section 3.1.1 to incorporate Visit 10 for nonpregnant women in Stage 1 who received a booster dose • Updated Sections 3.2.1, 3.2.2, 3.3.1, 3.3.2, 3.3.3, and 3.3.4 to incorporate changes related to immunogenicity endpoints • Updated Sections 3.4.1, 3.6.1, 3.6.2, and 3.6.2.2 to specify that information will be collected following primary and booster vaccinations separately in Stage 1	Based on Protocol Amendment 6 and team discussions

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
	• Updated Section 3.6.1 to incorporate Visit 10 for nonpregnant women in Stage 1 who received a booster dose • Updated Section 3.7.2.1 to incorporate Visit 10 for nonpregnant women in Stage 1 who received a booster dose • Updated Section 3.7.2.1 to specify that medications taken to treat AEs were recorded following both primary and booster vaccinations for nonpregnant women in Stage 1 • Updated Section 4.2.1 to distinguish primary and booster vaccination mITT populations • Updated Section 4.3 to specify that safety data for nonpregnant women (Stage 1) will be summarized separately for primary and booster vaccinations • Updated Section 5.2 to specify that the GBS6 IgG antibody levels will be standardized • Updated Section 5.2.3 to specify i) that the associations between IgG and OPA as well as CCI and OPA are not listed as potentially investigated and ii) that the association between CCI and IgG will now be limited to Stage 2 only instead of Stages 2 and 3 • Updated Section 5.3.1 to incorporate corrections on lower limit of quantitation (LLOQ) for IgG and to include standardized quantitated values • Updated Section 6.1.1.4 to incorporate Visit 10 for nonpregnant women in Stage 1 who received a booster dose • Updated Sections 5.2, 5.2.1.3, 5.2.2.5, 6.1.1, 6.2.1.1, 6.3.1.2, 6.3.1.3, 6.3.1.4, 6.6.1.1, and 6.6.2.1 to clarify the number of vaccine groups within each summary of results • Updated Sections 6.2.1.2, 6.3.2.1, and 6.3.2.2 to incorporate the fact that there was only one vaccine group for booster vaccination • Updated Sections 6.2.1, 6.3.1, 6.3.2, 6.3.3, 6.3.4, 6.3.5, 6.4, and 6.5 to incorporate changes related to immunogenicity endpoints	

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
	• Updated Section 7.2 to specify that safety and immunogenicity data from maternal and infant participants from Stage 2 and Stage 3 will be analyzed separately • Updated Sections 5.2 and 7.2 to specify that immunogenicity data from Stage 3 will also be analyzed separately by country (USA/UK, South Africa) • Updated Tables 9, 10, and 11 to incorporate changes in immunogenicity endpoints	
Amendment 4 5.0	• Added minor editorial changes throughout the document to improve clarity • Updated Section 2.1.3.2 to specify that the immune response diphtheria and 13-valent pneumococcal conjugate vaccine administered to infant participants delivered to maternal participants enrolled in the study and vaccinated with GBS6 will be analyzed in South Africa only • Updated Section 2.2.3 and Table 2 to reduce the number of maternal participants to be enrolled in Stage 3 from 200 to approximately 36 for USA only • Updated Section 4.1.2 to specify that blood will be collected within 72 hours after delivery if the maternal participant does not have the 1-month postvaccination visit • Updated Sections 3.3.3, 6.3.4.2, 6.3.4.5 and 6.3.4.6 to be aligned with the protocol • Updated Section 3.6.4.2 to clarify the analysis of CCI [redacted]	Based on Protocol Amendment 7

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C1091002. A brief description of the study design and the study objectives are given below. Subsequent sections describe analysis populations and give the definitions of the safety and immunogenicity endpoints followed by details of statistical reporting. A list of tables, listings, and figures, mock-up tables, listings, and figures, and programming rules are prepared separately based on the methods described in this document. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

2.1.1. Primary Objectives

2.1.1.1. Primary Objective: Stage 1

- To describe the safety and tolerability of various group B streptococcus 6-valent polysaccharide conjugate vaccine (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.

2.1.1.2. 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.

2.1.1.3. 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.

2.1.2. Secondary Objectives

2.1.2.1. Secondary Objective: 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.

2.1.2.2. Secondary Objective: Stage 2

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

2.1.2.3. Secondary Objective: Stage 3

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

2.1.2.4. 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.

2.1.3. Exploratory Objectives

2.1.3.1. Exploratory Objectives: Stage 1

CCI [redacted]

2.1.3.2. Exploratory Objectives: Stages 2 and 3

CCI [redacted]

2.1.3.3. Exploratory Objectives: Stages 1, 2, and 3

CCI

[redacted]

2.2. Study Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of a multivalent GBS6 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. A total of approximately 622 participants (66 nonpregnant women and 556 maternal participants and their infants) will be enrolled in this study.

2.2.1. 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 capsular polysaccharide [CPS]/serotype/dose) with or without aluminum phosphate ($AlPO_4$) (see Table 2).

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.

2.2.2. 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. Pregnant women, once consented, will be referred to as "maternal participants". The first 42 eligible maternal participants at each dose level will compose a 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. Further enrollment will be expanded at each dose level until 78 additional participants are enrolled (expanded cohort).

Approximately 360 maternal participants are planned to be enrolled in Stage 2 (see Table 2).

2.2.3. Stage 3

Approximately 196 additional maternal participants will be enrolled in Stage 3 to receive asingle dose/formulation of the selected GBS6 or placebo (saline control) in a 1:1 ratio (see Table 2).

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

Stage 1 Dose/Formulation Group[a] (Nonpregnant Women)		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 (Maternal Participants)		**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 (Maternal Participants)		**Total (1:1)**		
Selected Dose	Selected GBS6 dose/formulation	98		
	Placebo (saline control)	98		

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

a. Stage 1 participants (nonpregnant women) willing and eligible to participate returned 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.

For additional details on the types of data being collected at each visit within each stage, refer to Section 1 of the protocol.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Endpoints: Nonpregnant Women (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 through approximately 7 to 12 months following the booster dose of investigational product.

3.1.2. Primary 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 and delivery mode.

3.1.3. Primary 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 Endpoints

3.2.1. Secondary Endpoints: Nonpregnant Women (Stage 1)

- GBS6 serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) 1 month after the primary vaccination in nonpregnant women.
- GBS6 serotype-specific IgG GMCs measured before and 1 month, 3 months, and 6 months after a booster vaccination in nonpregnant women.

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

- GBS6 serotype-specific IgG GMCs measured at 2 weeks and 1 month after vaccination and at delivery in maternal participants.
- GBS6 serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) measured 1 month after vaccination and at delivery in maternal participants.

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

- GBS6 serotype-specific IgG GMCs in infant participants measured at birth.
- GBS6 serotype-specific OPA GMTs in infant participants measured at birth.

3.3. Exploratory Endpoints

3.3.1. Exploratory Endpoints: Nonpregnant Women (Stage 1)

CCI

[redacted]

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

CCI

[redacted]

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

CCI [redacted]

3.3.4. Exploratory Endpoints: Maternal and Infant Pairs (Stages 2 and 3)

CCI [redacted]

3.4. Baseline and Other Variables

Nonpregnant Women: Stage 1

Day 1 is defined as the day of vaccination and start of the reporting period for local reactions and systemic events in the electronic diary (e-diary).

Day 1 is considered the baseline visit for the following assessments: immunogenicity, CCI [redacted], and vital signs.

Day 1 before the first vaccination (primary series) is defined as the primary vaccination baseline visit. Prebooster Day 1 is defined as the booster vaccination baseline visit.

Maternal Participants: Stages 2 and 3

Day 1 is defined as the day of vaccination and start of the reporting period for local and systemic reactions in the e-diary.

Prior to vaccination, on Day 1, a baseline assessment of systemic events (nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain over the previous month) will be recorded in the e-diary.

Day 1 is considered the baseline visit for the following assessments: immunogenicity, CCI [redacted], systemic events prior to vaccination, physical examination, obstetric examination, and vital signs.

Maternal Participants: Stage 2 Sentinel Cohort

Laboratory (hematology and chemistry) data will be collected for sentinel-cohort maternal participants only. Data are collected during the screening visit, Visit 0 (-14 to -2 days prior to vaccination), and will be considered baseline data. For participants with a rescreening visit, the rescreening laboratory results will be considered as the baseline data.

Infant Participants: Stages 2 and 3

Day 1 is defined as the day of birth (Visit 1) for the infant participants, which corresponds to Visit 4 (delivery visit) for maternal participants.

Day 1 is considered the baseline visit for the following assessments: immunogenicity, CCI [redacted], physical examination, and vital signs.

If Day 1 is not available for noninfant participants, the most recent available data before vaccination will be considered as the baseline data.

3.4.1. Demographics and Medical History: Nonpregnant Women (Stage 1)

Demographic variables collected include race, ethnicity, racial designation, and date of birth. In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis. Age at time of vaccination (in years) will be derived based on birthday. For example, if the vaccination date is 1 day before the participant's 19th birthday, the participant is 18 years old.

Medical history of clinical significance will be collected and categorized according to the current version (at the time of reporting) of the Medical Dictionary for Regulatory Activities (MedDRA).

Demographics and medical history will be collected for primary and booster vaccinations separately.

3.4.2. Demographics, Substance Use, Medical History, and Obstetric History: Maternal Participants (Stages 2 and 3)

Demographic variables collected include race, ethnicity, racial designation, and date of birth. Age at time of vaccination (in years) will be derived based on birthday. For example, if the vaccination date is 1 day before the participant's 19th birthday, the participant is 18 years old.

Alcohol and tobacco usage data will be collected at screening (Visit 0).

Medical history of clinical significance will be collected and categorized according to the current version (at the time of reporting) of MedDRA.

Obstetric history of clinical significance, including history from prior and current pregnancy(ies), will be collected and includes the following: number of previous pregnancies, live births, still deliveries, vaginal deliveries, cesarean deliveries, spontaneous abortions, elective terminations, ectopic pregnancies, previous neonatal deaths, and number of pregnancies that result in obstetrical complications. In case of obstetrical complications, the following data will be collected: result in a live birth (yes, no), preterm delivery (yes, no), singleton or multiple birth, unplanned cesarean delivery (yes, no), gestational age at birth or loss (weeks, days), polyhydramnios or oligohydramnios (yes, no), intrauterine growth

retardation or fetal growth restriction (yes, no), antepartum hemorrhage (yes, no), postpartum hemorrhage (yes, no), incompetent cervix (yes, no), prolonged labor (yes, no), other maternal complications (specify), fetal/neonatal congenital anomaly (yes, no), low birth weight (yes, no), and other obstetric history (specify).

Fetal ultrasound will be performed and recorded at the screening visit (Visit 0). The findings collected include: current gestational age (weeks, days), fetal growth for gestational age (normal, abnormal), fetal mobility (normal, abnormal), fetal morphology (normal, abnormal), amniotic fluid index, amniotic fluid (normal, abnormal), fetal position (normal, abnormal), placenta status (normal, abnormal), abdominal circumference (cm), and any significant findings (specify).

3.4.3. Demographics and Feeding Information: Infant Participants (Stages 2 and 3)

Demography data collected at birth will include: sex, race, ethnicity, racial designation, and date of birth and time. Data on feeding modality (breast milk, formula, other; other: specify) will be collected at each postbirth time point.

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[redacted]

3.6. Safety Endpoints

3.6.1. Adverse Events

All AEs are collected on the case report form (CRF) for nonpregnant women (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3) and will be categorized according to the current version (at the time of reporting) of MedDRA. For nonpregnant women (Stage 1), AEs will be collected following the primary and booster vaccinations separately.

An immediate AE is defined as any AE that occurred within the first 30 minutes after administration of the investigational product for nonpregnant women (Stage 1) and maternal participants (Stages 2 and 3) (see Section 8.8.2 [Immediate Adverse Events] of the protocol).

An MAE is defined as a nonserious AE that results in an evaluation at a medical facility. MAEs will be assessed from screening up to Visit 4 for nonpregnant women (Stage 1), from screening 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 up to Visit 10.

AEs of special interest for infant participants (Stages 2 and 3) are major congenital anomalies, developmental delay, and suspected or confirmed GBS infection and are collected from birth through the end of the study (12-month postbirth visit). GBS infections that occurred during Days 1 through 7 are referred to as early-onset disease (EOD) and those that occurred during Days 8 through 90 are referred to as late-onset disease (LOD), where Day 1 is the day of birth.

AEs and SAEs will be captured and reported in accordance with Pfizer reporting standards and following the time period of collection outlined in Section 9.1.4 (Table 8) of the protocol.

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

- Tier 1 events: These are prespecified events of clinical importance and, if any, are maintained in a list in the product's Safety Surveillance Review Plan. There are no preidentified Tier 1 events for this study.
- Tier 2 events: These are events that are not Tier 1 but are "common." A MedDRA preferred term is defined as a Tier 2 event if there are 4 or more participants in at least 1 vaccine group.
- Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

3.6.2. Reactogenicity Data

Reactogenicity data are solicited AEs collected using an e-diary for all nonpregnant women (Stage 1) and maternal participants (Stages 2 and 3) during Days 1 through 7, starting on the day of vaccination (Day 1 [Visit 1]). For nonpregnant women (Stage 1), reactogenicity data are collected following the primary and booster vaccinations separately.

3.6.2.1. Local Reactions

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

Presence of Local Reactions (Proportion of Participants Reporting)

The participant will record the presence or absence of pain at the injection site in the e-diary as 'Mild,' 'Moderate,' 'Severe,' or 'None.' The presence or absence of redness or swelling will be recorded as 'Yes' or 'No.' Additionally, if redness or swelling is present, then the participant will measure the largest diameter and record the measurement rounded up to the

nearest whole number in measuring device units (range: 1 to 21+). Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 centimeters. A participant with a severe (Grade 3 or above) local reaction will be prompted to contact the investigator to perform an unscheduled visit and assess the reaction.

Only an investigator is able to classify a participant's local reaction as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, telephone contact with the participant. If a participant experiences a Grade 4 local reaction, it will be captured as an AE in the unplanned visit CRF page. A severe local reaction entry in the e-diary that is later assessed as Grade 4 will be treated as a Grade 4 event in the analysis.

The presence or absence of each local reaction on a given day is defined as follows:

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

= 'Yes', if the participant reports the reaction as 'Yes' for redness or swelling **or** if the reaction is assessed as 'Mild,' 'Moderate,' 'Severe,' or 'Grade 4' for pain at the injection site on a given day;

= 'No', if the participant reports the reaction as 'No' for redness or swelling **or** 'None' for pain at the injection site on a given day.

For each local reaction, the derivation of whether or not the specific reaction occurred on "any day (Day 1-7)" will be made. The derivation of this variable is given in Table 3.

Table 3. Derived Variables for Each Local Reaction

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Day 1-7)	Participant reports the reaction as 'Yes' on any day (Day 1-7)	Participant reports the reaction as 'No' on all 7 days or as a combination of 'No' and missing on all 7 days.	Participant reports the reaction as missing on all 7 days.

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

For any local reaction on any day, a similar definition can be applied as given in Table 4.

Table 4. Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
Any day (Day 1-7)	Participant reports any local reaction as 'Yes' on any day during Days 1-7.	Participant reports the reaction as 'No' on all 7 days or as a combination of 'No' and missing on all 7 days for all 3 local reactions.	Participant reports all of the local reactions as missing on all 7 days.

Grading Scale for Local Reactions

The grading of local reactions is listed in Table 5.

Table 5. Local Reactions 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 event will not be collected in the e-diary but will be recorded as an AE on the CRF.
c. Prevents daily activity, ie, results in missed days of work or school or is otherwise incapacitating or includes use of narcotics for analgesia.

Maximum Severity for Local Reactions

The maximum severity (highest grading) of each local reaction within 7 days of vaccination will be derived. The maximum severity will be derived as follows:

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

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

= *highest grade* (maximum severity) within 7 days of vaccination if the answer is not 'No' for at least 1 day.

Duration of Each Local Reaction

The duration of each local reaction will be calculated in days as (resolution date of reaction – start date of reaction + 1). Resolution of the event is the last day on which the event is recorded in the e-diary or the date the event ends if it is unresolved during the participant diary-recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing. Participants with no reported reaction have no duration.

Onset of Local Reaction

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

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

For the onset day of any local reaction, the first day of reporting any severity of any local reaction will be counted.

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

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

3.6.2.2. Systemic Events

In addition to data from Days 1 through 7 for all nonpregnant women (Stage 1 – primary and booster vaccinations separately) and maternal participants (Stages 2 and 3), prior to vaccination on Day 1, a baseline assessment of systemic events will be recorded in the e-diary for the maternal participants (Stages 2 and 3).

Systemic events reported via e-diary are: fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain. The highest temperature for each day for 7 days after vaccination is recorded in the e-diary. The protocol defines fever as an oral temperature >38.0°C (≥100.4°F). For ongoing fever on Day 7, the stop date will be recorded in the CRF. Additionally, the participant is to document the presence or absence of remaining systemic events in the e-diary as 'Mild', 'Moderate', 'Severe', or 'None'. Participants are asked to assess the severity of each event according to Table 5. 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, it will be captured under the unplanned visit CRF page. A severe systemic event entry in the e-diary that later is assessed as Grade 4

will be treated as Grade 4 for analyses. For all ongoing systemic events on Day 7, the stop date will be recorded in the CRF.

Any temperature recorded as <35.0°C (<95.0°F) or >42.0°C (>107.6°F) will be treated as data entry errors and excluded from the analyses. For reporting purposes, fever will be analyzed using the following temperature ranges:

- ≥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)

Table 6. Systemic Events 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
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

Abbreviations: CRF = case report form; 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 events will not be collected in the e-diary but will be recorded as AEs on the CRF.
c. Prevents daily routine activity, ie, results in missed days of work or school or is otherwise incapacitating or includes use of narcotics for analgesia.

The presence or absence of each systemic event on a given day is defined as follows:

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

= 'Yes', if the participant reports a temperature ≥38.0°C (≥100.4°F) for fever or fever is assessed as 'Mild', 'Moderate', 'Severe', or 'Grade 4' for the remaining events on a given day;

= 'No', if the participant reports a temperature <38.0°C (<100.4°F) for fever or 'None' for the remaining events on a given day.

For each systemic event, the following variables will be derived:

1. Presence or absence of each systemic event on each day (up to Day 7) after vaccination.
2. Presence or absence of each systemic event on "any day (Day 1-7)" after vaccination.
3. Maximum severity of each systemic event on "any day (Day 1-7)" after vaccination.
4. Presence or absence of any systemic event on "any day (Day 1-7)" after vaccination.
5. Duration of each systemic event after vaccination.
6. Onset day of each systemic event after vaccination.
7. Onset day of any systemic event after vaccination.

The derivation of these variables is similar to the derivation of the variables for local reactions (Section 3.6.2.1). Any systemic event includes fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, or joint pain.

3.6.2.3. Use of Antipyretic/Pain Medication

The use and type of antipyretic and/or pain medication will be recorded in the e-diary for 7 days (Days 1-7) after vaccination.

The following variables will be derived similarly to the variables for local reactions:

1. Use of antipyretic/pain medication on each day (Days 1-7) after vaccination.
2. Use of antipyretic/pain medication on "any day (Day 1-7)" after vaccination.
3. Duration of use of antipyretic/pain medication after vaccination.
4. Onset day of antipyretic use after vaccination.

3.6.3. Laboratory Data

Laboratory data will be collected for the maternal participants (Stage 2 sentinel cohort) only at screening, at rescreening if applicable, and at Visit 2 (2-week follow-up visit). 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. In such cases, only the worst result will be used for summary. The parameters of interest at each visit are listed in Table 7.

Table 7. Laboratory Tests

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

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

The toxicity grading scale in Table 8 for maternal participants will be adapted, as appropriate at a specific time point (eg, based on the pregnancy status at the visit), for grading laboratory test abnormalities.[1] For the grading scale, second trimester is defined as 14 1/7 through 28 0/7 weeks' gestation and third trimester as 28 1/7 weeks' gestation through delivery.

Table 8. Hematology and Blood Chemistry Toxicity Grading Scale for Maternal Participants

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Female Hb, g/dL	Second trimester	9.7-14.8	9.0-9.6	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or life-threatening acute blood loss
	Change from baseline		1.6-2.0	2.1-4.5	4.6-5.0	>5.0
	Third trimester	9.5–15.0	9.0-9.4	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or life-threatening acute blood loss
	Change from baseline		1.6-2.0	2.1-4.5	4.6-5.0	>5.0

Table 8. Hematology and Blood Chemistry Toxicity Grading Scale for Maternal Participants

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Platelets high, 1000 cell/mm^3	Second trimester	155-409	410-499	500-749	750-1000	>1000
	Third trimester	146-429	430-499	500-749	750-1000	>1000
Platelets low, 1000 cell/mm^3	Second trimester	155-409	125-154	100-124	25-99	<25
	Third trimester	146-429	125-146	100-124	25-99	<25
WBC high, 1000 cell/mm^3	Second trimester	5.6-14.8	>14.8-16.0	>16.0-20.0	>20.0-25.0	>25.0 signs of septic shock
	Third trimester	5.9-16.9	>16.9-18.0	>18.0-20.0	>20.0-25.0	>25.0 signs of septic shock
WBC low, 1000 cell/mm^3	Second trimester	5.6-14.8	<5.5-3.5	<3.5-1.4	<1.4-1.0	<1.0 signs of septic shock
	Third trimester	5.9-16.9	<5.9-3.5	<3.5-1.4	<1.4-1.0	<1.0 signs of septic shock
Neutrophils (absolute neutrophil count), 1000 cell/mm^3	Second trimester	3.8-12.3	<3.8-2.0	<2.0-1.0	<1.0-0.5	<0.5
	Third trimester	3.9-13.1	<3.9-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils (absolute), 1000 cell/mm^3	Second trimester	0-0.6	>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic
	Third trimester	0-0.6	>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic
Monocytes (absolute), 1000 cell/mm^3	Second trimester	0.1-1.1	≤10% outside normal range	>10% outside range: clinical correlation may be necessary and grading according to it		
	Third trimester	0.1-1.4	≤10% outside normal range	>10% outside range: clinical correlation may be necessary and grading according to it		
Basophils (absolute), 1000 cell/mm^3	Second trimester	0-0.1	≤10% outside normal range	>10% outside range: clinical correlation may be necessary and grading according to it		
	Third trimester	0-0.1	≤10% outside normal range	>10% outside range: clinical correlation may be necessary and grading according to it		
Lymphocytes high (absolute), 1000 cell/mm^3	Second trimester	0.9-3.9	>3.9-5.0	>5.0		
	Third trimester	1.0-3.6	>3.6-5.0	>5.0		

Table 8. Hematology and Blood Chemistry Toxicity Grading Scale for Maternal Participants

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Lymphocytes low (absolute), 1000 cell/mm^3	Second trimester	0.9-3.9	<0.9-0.75	<0.75-0.5	<0.5-0.25	<0.25
	Third trimester	1.0-3.6	<1.0-0.75	<0.75-0.5	<0.5-0.25	<0.25
BUN, mg/dL	Second trimester	3-13	14-19	20-30	>30	Requires dialysis
	Third trimester	3-11	12-19	20-30	>30	Requires dialysis
Creatinine, mg/dL	Second trimester	0.4-0.8	0.9-1.2	1.3-1.6	1.7-2.5	>2.5 or requires dialysis
	Third trimester	0.4-0.9	1-1.2	1.3-1.6	1.7-2.5	>2.5 or requires dialysis
AST, U/L	Second trimester	3-33	>1.0-1.2 x ULN	>1.2-3.0 x ULN	>3.0-8.0 x ULN	>8.0 x ULN cirrhosis transplant candidate
	Third trimester	4-32	>1.0-1.2 x ULN	>1.2-3.0 x ULN	>3.0-8.0 x ULN	>8.0 x ULN cirrhosis transplant candidate
ALT, U/L	Second trimester	2-33	>1.0-1.2 x ULN	>1.2-3.0 x ULN	>3.0-8.0 x ULN	>8.0 x ULN cirrhosis transplant candidate
	Third trimester	2-25	>1.0-1.2 x ULN	>1.2-3.0 x ULN	>3.0-8.0 x ULN	>8.0 x ULN cirrhosis transplant candidate
Total bilirubin (with increased LFTs), mg/dL	Second trimester	0.1-0.8	>1.0-1.2 x ULN	>1.2-1.5 x ULN	>1.5-1.8 x ULN	>1.8 x ULN
	Third trimester	0.1-1.1	>1.0-1.2 x ULN	>1.2-1.5 x ULN	>1.5-1.8 x ULN	>1.8 x ULN
Total bilirubin (with normal LFTs), mg/dL	Second trimester	0.1-0.8	>1.0-1.5 x ULN	>1.5-2.0 x ULN	>2.0-3.0 x ULN	>3.0 x ULN
	Third trimester	0.1-1.1	>1.0-1.5 x ULN	>1.6-2.0 x ULN	>2.0-3.0 x ULN	>3.0 x ULN
Alkaline phosphatase, U/L	Second trimester	25-126	>1.0-1.2 x ULN	>1.2-3.0 x ULN	>3.0-8.0 x ULN	>8.0 x ULN
	Third trimester	38-229	>1.0-1.2 x ULN	>1.2-3.0 x ULN	>3.0-8.0 x ULN	>8.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Hb = hemoglobin; LFT = liver function test; ULN = upper limit of normal; WBC = white blood cell.

3.6.4. Physical Examination, Including Vital Signs

3.6.4.1. Physical Examination, Including Vital Signs: Nonpregnant Women (Stage 1)

Physical examination will be performed at the screening visit (Visit 0) for primary vaccination and at the screening visit (Visit 5) for booster vaccination. The results will be recorded as normal, abnormal, or not done in the CRF.

Vital signs, including weight, height, sitting systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature, will be measured at the screening visit (Visit 0), prior to vaccination on Day 1 (Visit 1) for primary vaccination, and at the screening visit (Visit 5) for booster vaccination and recorded in the CRF.

3.6.4.2. Physical Examination, Including Vital Signs: Maternal Participants (Stages 2 and 3)

Physical examination will be performed at the screening visit (Visit 0), and results will be recorded as normal, abnormal, or not done in the CRF. Targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit, will be performed at Day 1 (Visit 1), the 2-week follow-up (Visit 2), the 1-month follow-up (Visit 3), and 6 weeks after delivery (Visit 6). Abnormal results, including those that indicate worsening of medical history conditions, will be recorded in the AE CRF.

Vital signs, including weight, sitting systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature, will be measured at the screening visit (Visit 0), prior to vaccination on Day 1 (Visit 1), the 2-week follow-up (Visit 2), and the 1-month follow-up (Visit 3) and recorded in the CRF. Height will only be measured and recorded at the screening visit. Body mass index (BMI) will be calculated as weight in kilograms/(height in meters)^2 using the height and weight collected at the screening visit.

3.6.4.3. Physical Examination, Including Vital Signs: Infant Participants (Stages 2 and 3)

Physical examination will be performed at birth (Visit 1), 6 weeks after delivery (Visit 3), 14 weeks after delivery (Visit 4), 18 weeks after delivery (Visit 5), and 12 months after delivery (Visit 7), and results will be recorded as normal, abnormal, or not done in the CRF.

Vital signs, including weight, height (length at Visit 1), head circumference, pulse rate, respiratory rate, and axillary temperature, will be measured at birth (Visit 1), 6 weeks after delivery (Visit 3), 14 weeks after delivery (Visit 4), 18 weeks after delivery (Visit 5), and 12 months after delivery (Visit 7) and recorded in the CRF.

3.6.5. Obstetric Examination and Pregnancy Outcome: Maternal Participants (Stages 2 and 3)

Obstetric examination findings will be collected from screening (Visit 0) through the 1-month follow-up visit (Visit 3) and include the following: last menstrual period start date, certainty of menstrual start date (certain, uncertain, unknown), first and second trimester ultrasound dates, gestational age, method used to determine gestational age (last menstrual period, first trimester ultrasound, second trimester ultrasound, third trimester ultrasound, fundal height), estimated due date, vaginal examination status (normal, abnormal), fundal height (cm), fetal heart rate (beats/min), fetal movements (yes, no), investigator's assessment of fetal movement (normal, abnormal), fetal presentation (cephalic position, breech position, transverse position, unknown), and scars from previous deliveries (yes, no).

The following information regarding pregnancy outcome will be collected: date of delivery, location of delivery (medical facility, home, other), mode of delivery (vaginal, cesarean section), cesarean type (elective, semi-elective, emergency), delivery complications (yes, no), number of births, outcome at delivery (full-term live birth, premature live birth, stillbirth, spontaneous abortion, induced/elective abortion), gross visual inspection of the aborted fetus/stillbirth (not done, no observed abnormalities, observed abnormalities), and pathology performed (yes, no).

3.6.6. Birth Outcome: Infant Participants (Stages 2 and 3)

Infant outcome at birth will be collected at the delivery visit and include the following: gestational age (weeks, days), appearance, pulse, grimace, activity, and respiration (Apgar) score at 1, 5, and 10 minutes, Ballard score, infant cry immediately after delivery (yes, no), infant suckle shortly after delivery (yes, no), newborn normal (yes, no), congenital malformation/anomaly (yes, no), and other neonatal problem/abnormality (yes, no).

Also, infant vital status (live, neonatal death) will be derived using the response to "delivery outcome" from the pregnancy outcome and death information from the AE data. Neonatal death is defined as the death of a live born infant that occurred within 30 days of birth.

3.7. Study Conduct

3.7.1. E-Diary Completion

On each day, nonpregnant women and maternal participants are expected to complete all questions (the 3 local reactions, the 7 systemic events [including fever], and the use of antipyretic medication) in the e-diary. E-diary data will be transmitted and considered complete if all expected data on each day are available (ie, not missing). The data could be missing in the e-diary for a specific day, in which case it will not be transmitted and will be considered incomplete. All the data reported on the e-diary will be transferred electronically to the e-diary vendor.

3.7.2. Nonstudy Vaccines and Concomitant Treatments

Nonstudy vaccines and concomitant medications will be categorized according to the latest version of the World Health Organization (WHO) Drug Dictionary.

3.7.2.1. Nonstudy Vaccines and Concomitant Treatments: Nonpregnant Women (Stage 1)

Any nonstudy vaccinations given from the signing of the informed consent document (ICD) to the 1-month follow-up for the primary vaccination (Visit 3) and from the signing of the ICD (Visit 5) to the 1-month follow-up for the booster vaccination (Visit 7) will be recorded in the CRF.

Any medications taken from the signing of the ICD through the 1-month follow-up for the primary vaccination (Visit 3) and from the signing of the ICD (Visit 5) to the 1-month follow-up for the booster vaccination (Visit 7) will be recorded in the CRF. Additionally, any medications taken to treat AEs from the signing of the ICD through the 6-month follow-up for the primary vaccination (Visit 4) and from the signing of the ICD (Visit 5) through Visit 10 for the booster vaccination will be recorded in the CRF.

3.7.2.2. Nonstudy Vaccines and Concomitant Treatments: Maternal Participants (Stages 2 and 3)

Any nonstudy vaccinations given from the signing of the ICD to delivery (Visit 4) will be recorded in the CRF.

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

3.7.2.3. Nonstudy Vaccines and Concomitant Treatments: Infant Participants (Stages 2 and 3)

Any nonstudy vaccinations received from birth (Visit 1) to the 12-month postbirth follow-up visit (Visit 7) will be recorded in the CRF.

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

4. ANALYSIS SETS

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

For 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.

4.1. Per-Protocol Analysis Set

In this study, the per-protocol analysis set will be referred to as the evaluable immunogenicity population. The evaluable immunogenicity population will be the primary population for all immunogenicity data analyses.

The immunogenicity data based on the evaluable immunogenicity population for nonpregnant women (Stage 1), and maternal participants (Stages 2 and 3) will be summarized according to the vaccine group as administered, which by the population definition is equivalent to the vaccine group as randomized. The immunogenicity data for infant participants (Stages 2 and 3) will be summarized according to the vaccine group as administered to their mothers.

4.1.1. Per-Protocol Analysis Set: Nonpregnant Women (Stage 1)

The primary vaccination evaluable immunogenicity population will include participants who:

- Are eligible (have signed informed consent and met all inclusion/exclusion criteria) and randomized into the study;
- Have received GBS6 or placebo as randomized;
- Have blood drawn for assay testing within 27 to 49 days, inclusive, after primary vaccine administration at Visit 3 (1 month after vaccination);
- Have at least 1 valid and determinate assay result for the 1-month post–primary vaccination visit;
- Have no major protocol violation as determined by the sponsor's global medical monitor.

The booster vaccination evaluable immunogenicity population will include participants who:

- Are eligible (have signed informed consent and met all inclusion/exclusion criteria) and assigned to the booster vaccination;
- Have received a booster dose of GBS6;

- Have blood drawn for assay testing within 27 to 49 days, inclusive, after booster vaccine administration at Visit 7 (1 month after booster vaccination);
- Have at least 1 valid and determinate assay result for the 1-month after the booster vaccination visit;
- Have no major protocol violation as determined by the sponsor's global medical monitor.

Major protocol violations will be determined by clinical review. A major protocol violation is a protocol violation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's global medical monitor will identify those participants with protocol violations before any immunogenicity analysis is carried out.

4.1.2. Per-Protocol Analysis Set: Maternal Participants (Stages 2 and 3)

The evaluable immunogenicity population will include participants who:

- Are eligible (have signed informed consent and met all inclusion/exclusion criteria) and randomized into the study;
- Have received GBS6 or placebo as randomized;
- Have blood drawn for assay testing within 27 to 49 days, inclusive, after vaccine administration at Visit 3 (1 month after vaccination) or within 72 hours after delivery at the delivery visit if the maternal participant does not have the 1-month postvaccination visit (and this happens before Day 49);
- Have at least 1 valid and determinate assay result for either the 1-month postvaccination or the delivery visit (if the maternal participant does not have the 1-month postvaccination visit);
- Have no major protocol violation as determined by the sponsor's global medical monitor.

Major protocol violations will be determined by clinical review as described in the previous section for nonpregnant women.

4.1.3. Per-Protocol Analysis Set: Infant Participants (Stages 2 and 3)

The evaluable immunogenicity population will include participants:

- Who are eligible (mother has signed informed consent and met all inclusion/exclusion criteria) and whose mother was randomized into the study. If the mother is not eligible for the study, her infant(s) will not be eligible for the study as well.

- Whose mother has received GBS6 or placebo as randomized;
- Who have cord blood available, or blood drawn for assay testing within 72 hours after birth (Visit 1);
- Who have at least 1 valid and determinate assay result at the birth visit (Visit 1);
- Who have no major protocol violation as determined by the sponsor's global medical monitor.

4.1.4. Per-Protocol Analysis Set: Maternal and Infant Pairs (Stages 2 and 3)

This evaluable immunogenicity population will include the maternal and infant pairs who are in their respective evaluable immunogenicity populations.

4.2. Full Analysis Set

In this study, the full analysis set will be referred to as the mITT population.

The immunogenicity data based on the mITT population for nonpregnant women (Stage 1), and maternal participants (Stages 2 and 3) will be summarized according to the vaccine group as randomized. The immunogenicity data for infant participants (Stages 2 and 3) will be summarized according to the vaccine group as randomized to their mothers.

The immunogenicity results based on the mITT population will be summarized for secondary immunogenicity endpoint(s) within each stage of the study only if there is a sizable difference (eg, ~10%) in the number of participants between the mITT and evaluable immunogenicity populations. CCI [redacted]

4.2.1. Full Analysis Set: Nonpregnant Women (Stage 1)

The primary vaccination mITT population will include all randomized participants who have at least 1 valid and determinate assay result.

The booster vaccination mITT population will include all randomized participants who received a booster dose and have at least 1 valid and determinate assay result.

4.2.2. Full Analysis Set: Maternal Participants (Stages 2 and 3)

All randomized participants who have at least 1 valid and determinate assay result will be included in the mITT population.

4.2.3. Full Analysis Set: Infant Participants (Stages 2 and 3)

All infants of randomized maternal participants who have at least 1 valid and determinate assay result will be included in the mITT population.

4.3. Safety Analysis Set

In this study, the safety analysis set will be referred to as the safety population. A safety population will be defined separately for nonpregnant women and maternal participants and their infant participants. The safety population is the analysis population for all the safety endpoints.

The safety data for nonpregnant women with primary and booster vaccinations (Stage 1) and maternal participants (Stage 2 and 3) will be summarized according to the vaccine group as administered. The safety data for infant participants (Stages 2 and 3) will be summarized according to the vaccine group as administered to their mothers.

4.3.1. Safety Analysis Set: Nonpregnant Women (Stage 1)

All participants who received a primary dose of GBS6 vaccine or placebo will be included in the primary vaccination safety population.

All participants who received a booster dose of GBS6 will be included in the booster vaccination safety population.

4.3.2. Safety Analysis Set: Maternal Participants (Stages 2 and 3)

All participants who received the GBS6 vaccine or placebo will be included in the safety population.

4.3.3. Safety Analysis Set: Infant Participants (Stages 2 and 3)

All infants whose mother received the GBS6 vaccine or placebo will be included in the safety population.

4.4. Other Analysis Sets

No other analysis sets will be defined in this study.

4.5. Vaccine Misallocations

- Randomized but not vaccinated: this group includes nonpregnant women (Stage 1) and maternal participants (Stages 2 and 3) who were randomized but not vaccinated and infant participants (Stages 2 and 3) whose mothers were randomized but not vaccinated. These participants will not be included in the safety population for safety analyses. These participants will not be included in the evaluable immunogenicity population, but they will be included in the mITT population for immunogenicity analyses for participants with valid and determinant assay results. The immunogenicity results for these participants will be reported under the vaccine group as randomized or as their mothers were randomized in the case of infant participants.

- Vaccinated but not randomized: this group includes nonpregnant women (Stage 1) and maternal participants (Stages 2 and 3) who were vaccinated but not randomized and infant participants (Stages 2 and 3) whose mothers were vaccinated but not randomized. These participants will be included in the safety population for safety analyses and will be reported under the vaccine group based on the vaccine they received, or the vaccine received by their mothers in the case of infant participants. They will be excluded from immunogenicity analyses based on either the evaluable immunogenicity or mITT population.

- Randomized but received incorrect vaccine: this group includes nonpregnant women (Stage 1) and maternal participants (Stages 2 and 3) who were randomized but received an incorrect vaccine and infant participants (Stages 2 and 3) whose mothers were randomized but received an incorrect vaccine. These participants will be included in the mITT population for immunogenicity analyses if any assay results are available and will be reported under the vaccine group based on their or their maternal (for infants) randomized vaccine group in the analysis. These participants will also be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine they or their mothers (for infants) received. These participants will be excluded from the evaluable immunogenicity population for immunogenicity analyses.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Statistical Hypotheses

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. In all 3 stages of the study, no formal statistical hypothesis testing will be performed. An estimation approach will be used to assess the safety and immunogenicity objectives.

5.1.2. Statistical Decision Rules

Statistical decision rules will not be utilized in this study. All analyses are considered descriptive in nature.

5.2. General Methods

Descriptive summary statistics will be provided for all endpoints. Unless otherwise explicitly stated, the descriptive statistics for continuous variables are: n, mean, median, standard deviation, minimum, and maximum. The descriptive statistics for categorical variables are: the proportion (%), n (the numerator), and N (the denominator) used in the proportion calculation.

The dose/formulation level and vaccine group (hereafter referred to as vaccine group) in this study are defined as below:

1. GBS6 (5 µg)/$AlPO_4$
2. GBS6 (5 µg)/no $AlPO_4$
3. GBS6 (10 µg)/$AlPO_4$
4. GBS6 (10 µg)/no $AlPO_4$
5. GBS6 (20 µg)/$AlPO_4$
6. GBS6 (20 µg)/no $AlPO_4$
7. Placebo

All safety and immunogenicity summaries in each stage of the study will be presented by a subset or complete set dependent on the study stage. In Stage 1 for primary vaccination, the subset will only include Groups 5 through 7; Stage 1 for booster vaccination will only include GBS6 (20 µg)/$AlPO_4$; Stage 2 will include all vaccine groups; Stage 3 will only include GBS6 (20 µg)/no $AlPO_4$ and placebo. Unless otherwise explicitly stated, all Stage 2 maternal participants from both sentinel and expanded cohorts will be combined, by vaccine groups listed above. Similarly, all Stage 2 infant participants from both sentinel and expanded cohorts will be combined according to their mother's vaccine group.

Both safety and immunogenicity results will be summarized separately for nonpregnant women with primary vaccination (Stage 1), nonpregnant women with a booster vaccination (Stage 1), maternal participants in Stage 2, maternal participants in Stage 3, infant participants in Stage 2, and infant participants in Stage 3. Immunogenicity data from Stage 3 will also be summarized separately by country (USA/UK, South Africa).

The GBS6 IgG antibody levels will be standardized as current quantitated values × correction factor. The lower limit of quantitation (LLOQ) values will be standardized as LLOQ = LLOQ × correction factor. The correction factors are set as follows: Ia, 0.46628125; Ib, 0.463392157; II, 1.451696809; III, 0.727236264; IV, 0.686258373; and V, 0.236850746. The standardized quantitated values will be reported for all analyses.

5.2.1. Analyses for Binary Data

5.2.1.1. Immunogenicity Data

CCI [redacted]

CCI [redacted]

The exact CIs for a proportion will be computed using the F distribution. If r is the number of responses and n is the number of participants, then it follows that $p = r / n$ is the estimate of the proportion of responses. An exact 95% CI can be computed by solving the following 2 equations. For the lower limit P_L, use

$$p_L = \frac{rF_L}{(rF_L + (n - r + 1))}$$

and for the upper limit P_U, use

$$p_U = \frac{(r+1)F_U}{(n-r) + (r+1)F_U}$$

where F_L is the quantile from the F distribution for α=0.025, with numerator degrees of freedom equal to 2r and denominator degrees of freedom equal to 2(n-r+1). F_U is the quantile from the F distribution for α=0.975, with numerator degrees of freedom equal to 2(r+1) and denominator degrees of freedom equal to 2(n-r). When r equals 0, F_L should be set equal to 1.0 so P_L equals 0. When r equals n, F_U should be set equal to 1.0 so P_U equals 1.

The CI using the F distribution is described by Collett (1991).[3]

CCI [redacted]

5.2.1.3. Safety Data

Similarly, the exact 2-sided 95% CIs using the Clopper and Pearson method will be provided by vaccine group for all primary safety endpoints, proportions of participants reporting local reactions, systemic events (Stage 1 nonpregnant women with primary vaccination [3 vaccine groups], Stage 1 nonpregnant women with booster vaccination [1 vaccine group], Stage 2 maternal participants [7 vaccine groups], and Stage 3 maternal participants [2 vaccine groups]), AEs, SAEs, and MAEs (Stage 1 nonpregnant women with primary vaccination

[3 vaccine groups], Stage 1 nonpregnant women with booster vaccination [1 vaccine group], Stage 2 maternal participants [7 vaccine groups], and Stage 3 maternal participants [2 vaccine groups] and their infants), obstetric complications, delivery outcomes, and delivery mode (Stages 2 and 3 maternal participants), and AEs of special interest (Stages 2 and 3 infant participants).

For Tier 2 AEs only, 95% CIs for the difference in proportions between each GBS6 vaccine group and placebo (risk difference) based on the Chan and Zhang[4] method will be provided for nonpregnant women with primary vaccination (Stage 1), nonpregnant women with booster vaccination (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3).

5.2.2. Analyses for Continuous Data

5.2.2.1. Geometric Means

The GBS6 serotype-specific IgG, CCI and OPA, and CCI , antibody levels at selected blood sampling time points will be summarized by geometric means (GMCs or GMTs) and the associated 2-sided 95% CIs by vaccine group. The GMCs (GMTs) will be calculated as the mean of the logarithmically transformed assay results and back transformed to its original units. The 2-sided 95% CIs will be constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results using Student's t distribution.

CCI

5.2.2.3. Geometric Mean Ratios

The GBS6 serotype-specific antibody level ratios of infant to mother IgG (CCI) will be summarized by vaccine group at the birth/delivery blood sampling time point by geometric means and associated 2-sided 95% CIs. The antibody levels are logarithmically transformed for analysis. The geometric mean ratios (GMRs) are then calculated as the mean of the difference of logarithmically transformed measures. The GMRs and the associated 2-sided 95% CIs are then calculated CCI

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical reverse cumulative distribution curves (RCDCs) will be presented graphically by plotting the proportion of participants with the GBS6 serotype-specific antibody level equal to or exceeding the specified antibody level vs the indicated antibody level for each serotype separately by vaccine group and at a specific blood sampling time point (eg, 1 month after vaccination for nonpregnant women) for participants from different stages. The RCDCs at other time points may be generated. The LLOQ and/or defined threshold values will be marked on the horizontal axis.

5.2.2.5. Antibody Response Curves

Antibody response will be graphed for IgG concentrations by vaccine group at blood sampling time points from before vaccination (Day 1) to after vaccination for nonpregnant women with primary vaccination (Stage 1 [3 vaccine groups]), nonpregnant women with a booster vaccination (Stage 1 [1 vaccine group]), and maternal participants (Stage 2 [7 vaccine groups] and Stage 3 [2 vaccine groups]) and similarly for infant participants (Stages 2 and 3) by their mother's vaccine group at birth and postbirth blood sampling time points. The curves will display the geometric mean and 95% CI at each of the time points with a line connecting the geometric means for each vaccine group across time.

Antibody response will also be graphed for OPA titers by vaccine group at blood sampling time points from before vaccination (Day 1) to after vaccination for maternal participants (Stage 2 [7 vaccine groups] and Stage 3 [2 vaccine groups]) and similarly for infant participants (Stages 2 and 3) by their mother's vaccine group at birth and postbirth blood sampling time points. The curves will display the geometric mean and 95% CI at each of the time points with a line connecting the geometric means for each vaccine group across time.

5.2.3. Other Analyses

A separate mixed-effects model with repeated measures (MMRM)[5] for maternal and infant participants will be utilized to assess the effects of regressors/covariates, such as vaccine group (maternal vaccine group for infant participants), visit (blood sampling time point), baseline or at-birth GBS6 serotype-specific IgG antibody level, sex (male, female, or undifferentiated as appropriate), age at vaccination (years), delivery outcome (preterm or full-term), CCI [redacted] on the associated GBS6 serotype-specific postvaccination or postdelivery IgG antibody levels. Details regarding the specific model used for maternal and infant participants are provided in Section 6.3.3.1 and Section 6.3.4.1, respectively. An unstructured covariance matrix will be used to account for intraparticipant correlation. In case the model does not converge, other covariance structures (eg, autoregressive, compound symmetry) will be explored. The baseline and postvaccination IgG antibody levels will be transformed into logarithmic scale for analysis.

CCI [redacted]

5.3. Methods to Manage Missing Data

5.3.1. Immunogenicity Data

Values recorded as insufficient sera (QNS), indeterminate results, or "Not Done" will be set to missing. No imputation will be done for these missing values.

CCI

The GBS6 IgG, CCI , and OPA antibody levels above LLOQ are considered accurate. Values below the LLOQ or denoted as below the limit of quantitation (BLQ) will be set to 0.5 × LLOQ.

The GBS6 IgG antibody levels will be standardized as current quantitated values × correction factor. The LLOQ values will be standardized as standardized LLOQ = LLOQ × correction factor. The correction factors are set as follows: Ia, 0.46628125; Ib, 0.463392157; II, 1.451696809; III, 0.727236264; IV, 0.686258373; and V, 0.236850746. The standardized quantitated values will be reported for all analyses.

5.3.2. Safety Data

Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in the Vaccine Statistics Rulebook.

5.3.2.1. Reactogenicity Data

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

The reactogenicity data are collected through the e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day is nonmissing. No missing reactogenicity data will be imputed other than what is described in Section 3.6.2.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Primary Endpoint(s): Nonpregnant Women (Stage 1)

6.1.1.1. Proportion of Nonpregnant Women Reporting Prompted Local Reactions Within 7 Days Following Administration of the Primary and Booster Investigational Product

The analysis will be performed for the primary and booster doses.

Endpoints: Maximum severity during the analysis time interval for pain at the injection site, redness, and swelling.

- Analysis time points: Days 1 through 7.
- Analysis population: Safety population for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The numerator (n), denominator (N) used for the calculation of proportion, proportion, and associated 2-sided exact 95% CI will be presented for each severity (mild, moderate, severe, and Grade 4) of each local reaction, by vaccine group (3 vaccine groups for primary vaccination and 1 vaccine group for booster vaccination).

Figures: None.

6.1.1.2. Proportion of Nonpregnant Women Reporting Prompted Systemic Events Within 7 Days Following Administration of the Primary and Booster Investigational Product

The analysis will be performed for the primary and booster doses.

Endpoints: Maximum severity during the analysis time interval for fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain.

- Analysis time points: Days 1 through 7.
- Analysis population: Safety population for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The numerator (n), denominator (N) used for the calculation of proportion, proportion, and associated 2-sided exact 95% CI will be presented for each severity (mild, moderate, severe, and Grade 4) of each systemic event, by vaccine group (3 vaccine groups for primary vaccination and 1 vaccine group for booster vaccination).

Figures: None.

6.1.1.3. Proportion of Nonpregnant Women Reporting AEs Through 1 Month Following Administration of the Primary and Booster Investigational Product

The analysis will be performed for the primary and booster doses.

Endpoints: AEs experienced by nonpregnant women (Stage 1).

- Analysis time points: Day 1 to 1 month after vaccination.
- Analysis population: Safety population for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AEs, SAEs, immediate AEs, severe AEs, related AEs, MAEs, and AEs leading to withdrawal, by vaccine group (3 vaccine groups for primary vaccination and 1 vaccine group for booster vaccination). Additionally, number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, each system organ class (SOC), and each preferred term within SOC, by vaccine group (3 vaccine groups for primary vaccination and 1 vaccine group for booster vaccination).
- Tier 2 AEs: The number of participants with AEs (n), proportion, risk difference, and associated 2-sided exact 95% CI will be presented for each preferred term.

Figures: None.

6.1.1.4. Proportion of Nonpregnant Women Reporting MAEs and SAEs Through 6 Months Following Administration of the Primary Dose and Through Approximately 7 to 12 Months Following Booster Investigational Product

The analysis will be performed for the primary and booster doses.

Endpoints: MAEs and SAEs experienced by nonpregnant women (Stage 1).

- Analysis time points: Day 1 through 6 months after primary vaccination and Day 1 through approximately 7 to 12 months after booster vaccination.
- Analysis population: Safety population for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AEs, SAEs, immediate AEs, severe AEs, related AEs, MAEs, and AEs leading to withdrawal, by vaccine group (3 vaccine groups for primary vaccination and 1 vaccine group for booster vaccination). Additionally, number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, each SOC, and each preferred term within SOC, by vaccine group (3 vaccine groups for primary vaccination and 1 vaccine group for booster vaccination), separately for all AEs, SAEs, related AEs, and MAEs.

Figures: None.

6.1.2. Primary Endpoint(s): Maternal Participants (Stages 2 and 3)

6.1.2.1. Proportion of Sentinel-Cohort Maternal Participants (Stage 2 Only) With Clinical Laboratory Abnormalities Following Administration of the Investigational Product at the 2-Week Follow-Up Visit

Endpoint: Abnormalities in safety laboratory parameters are based on the toxicity grading scale for pregnant women provided in Section 3.6.3.

- Analysis time point: Visit 2 (2 weeks after vaccination).
- Analysis population: Safety population for maternal participants (Stage 2 only).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The n and proportion will be presented for laboratory parameters (eg, hemoglobin, WBC) normal and for each grade (1 through 4), by vaccine group, for sentinel-cohort maternal participants from Stage 2 only.

Figures: None.

6.1.2.2. Proportion of Maternal Participants Reporting Prompted Local Reactions Within 7 Days Following Administration of the Investigational Product

Endpoints: Maximum severity during the analysis time interval for pain at the injection site, redness, and swelling.

- Analysis time points: Days 1 through 7.
- Analysis population: Safety population for maternal participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The numerator (n), denominator (N) used for the calculation of proportion, proportion, and associated 2-sided exact 95% CI will be presented for each severity (mild, moderate, severe, and Grade 4) of each local reaction, by vaccine group.

Figures: None.

6.1.2.3. Proportion of Maternal Participants Reporting Prompted Systemic Events Within 7 Days Following Administration of the Investigational Product

Endpoints: Maximum severity during the analysis time interval for fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain.

- Analysis time points: Days 1 through 7.
- Analysis population: Safety population for maternal participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The numerator (n), denominator (N) used for the calculation of proportion, proportion, and associated 2-sided exact 95% CI will be presented for each severity (mild, moderate, severe, and Grade 4) of each systemic event by vaccine group.

Figures: None.

6.1.2.4. Proportion of Maternal Participants Reporting AEs Through 1 Month After Administration of the Investigational Product

Endpoints: AEs experienced by maternal participants (Stages 2 and 3).

- Analysis time points: Day 1 to 1 month after vaccination.
- Analysis population: Safety population for maternal participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AEs, SAEs, immediate AEs, severe AEs, related AEs, MAEs, and AEs leading to withdrawal, by vaccine group. Additionally, the number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, each SOC, and each preferred term within SOC, by vaccine group.
- Tier 2 AEs: The number of participants with AEs (n), proportion, risk difference, and associated 2-sided exact 95% CI will be presented for each preferred term.

Figures: None.

6.1.2.5. Proportion of Maternal Participants With SAEs, MAEs, and Obstetric Complications Through the 12-Month Postdelivery Visit

Endpoints: MAEs, SAEs, and obstetric complications by pregnancy period (prepartum, intrapartum, and postpartum) experienced by maternal participants (Stages 2 and 3).

- Analysis time points: Day 1 to the 12-month postdelivery visit.
- Analysis population: Safety population for maternal participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AEs, SAEs, immediate AEs, severe AEs, related AEs, MAEs, AEs leading to withdrawal, and obstetric complications by pregnancy period (prepartum, intrapartum, and postpartum) by vaccine group. Additionally, the number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, each SOC, and each preferred term within SOC, by vaccine group, separately for all AEs, SAEs, related AEs, MAEs, and obstetric complications prepartum, intrapartum, and postpartum.

Figures: None.

6.1.2.6. Proportion of Maternal Participants With Each Delivery Outcome and Delivery Mode

Endpoints: Mode of delivery (vaginal, cesarean) and outcome at delivery (full-term live birth, premature live birth, stillbirth, spontaneous abortion, induced/elective abortion) for maternal participants (Stages 2 and 3).

- Analysis time point: Delivery visit.
- Analysis population: Safety population for maternal participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of participants (n), proportion, and associated 2-sided exact 95% CI for each category will be displayed by vaccine group.

Figures: None.

6.1.3. Primary Endpoint(s): Infant Participants (Stages 2 and 3)

6.1.3.1. Proportion of Infant Participants With Specific Birth Outcomes

Endpoints: Gestational age (weeks and days), Apgar scores at 1 and 5 minutes, Ballard score, newborn normal (yes, no), congenital malformation anomaly (yes, no), other neonatal problem/abnormality (yes, no), and vital status (live, neonatal death [a subset of live births], and stillbirth) for infant participants (Stages 2 and 3).

- Analysis time point: Delivery visit.
- Analysis population: Safety population for infant participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of participants (n), proportion, and associated 2-sided exact 95% CI for each category will be displayed by maternal vaccine group.

Figures: None.

6.1.3.2. Proportion of Infant Participants With AEs From Birth to 6 Weeks of Age

Endpoints: AEs experienced by infant participants (Stages 2 and 3).

- Analysis time points: Birth to 6 weeks of age.
- Analysis population: Safety population for infant participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AEs, SAEs, severe AEs, MAEs, and AEs leading to withdrawal, by maternal vaccine group. Additionally, the number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, each SOC, and each preferred term within SOC, by maternal vaccine group.
- Tier 2 AEs: The number of participants with AEs (n), proportion, risk difference, and associated 2-sided exact 95% CI will be presented for each preferred term.

Figures: None.

6.1.3.3. Proportion of Infant Participants With SAEs, AEs of Special Interest, and MAEs From Birth to 12 Months of Age

Endpoints: SAEs, AEs of special interest (major congenital anomalies, developmental delay, and suspected or confirmed GBS infection), and MAEs experienced by infant participants (Stages 2 and 3).

- Analysis time points: Birth to 12 months of age.
- Analysis population: Safety population for infant participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AEs, SAEs, severe AEs, MAEs, AEs leading to withdrawal, and AEs of special interest (major congenital anomalies, developmental delay, and suspected or confirmed GBS infection [overall, EOD, LOD]), by maternal vaccine group. Additionally, the number of participants with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented separately for any AE, each SOC, and each preferred term within SOC, by maternal vaccine group, separately for all AEs, SAEs, MAEs, major congenital anomalies, developmental delay, and suspected or confirmed GBS infection.

Figures: None.

6.2. Secondary Endpoint(s)

6.2.1. Secondary Endpoint(s): Nonpregnant Women (Stage 1)

6.2.1.1. GBS6 Serotype-Specific IgG GMCs Measured at 1 Month After the Primary Vaccination in Nonpregnant Women

Endpoints: GBS6 serotype-specific IgG antibody concentrations.

- Analysis time point: 1 Month after the primary vaccination.
- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) primary vaccination populations for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of participants with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented for each serotype, by vaccine group (3 vaccine groups).

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical RCDCs for 1 month after the primary vaccination time point will be generated separately for each serotype, by vaccine group (3 vaccine groups).

6.2.1.2. GBS6 Serotype-Specific IgG GMCs Measured Before and 1 Month, 3 Months, and 6 Months After the Booster Vaccination in Nonpregnant Women

Endpoints: GBS6 serotype-specific IgG antibody concentrations.

- Analysis time points: Before and 1 month, 3 months, and 6 months after the booster vaccination.
- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) booster vaccination populations for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of participants with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented for each serotype.

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical RCDCs for the time points before and 1 month, 3 months, and 6 months after the booster vaccination will be generated separately for each serotype.

6.2.2. Secondary Endpoint(s): Maternal Participants (Stages 2 and 3)

6.2.2.1. GBS6 Serotype-Specific IgG GMCs Measured at 2 Weeks and 1 Month After Vaccination and at Delivery in Maternal Participants

Endpoints: GBS6 serotype-specific IgG antibody concentrations.

- Analysis time points: 2 Weeks and 1 month after vaccination and at delivery.
- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) populations for maternal participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics and MMRM.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of participants with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented for each analysis time point and serotype, by vaccine group.
- GMCs and associated 95% CI from the MMRM analysis specified in Section 6.3.3.1.

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical RCDCs for the time points at 1 month after vaccination and at delivery will be generated separately for each serotype, by vaccine group.

6.2.2.2. GBS6 Serotype-Specific OPA GMTs Measured at 1 Month After Vaccination and at Delivery in Maternal Participants

Endpoints: GBS6 serotype-specific OPA antibody titers.

- Analysis time points: 1 Month after vaccination and at delivery.
- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) populations for maternal participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of participants with valid assay data (n), GMTs, and associated 2-sided 95% CI will be presented for each analysis time point and serotype, by vaccine group.

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical RCDCs for the time points at 1 month after vaccination and at delivery will be generated separately for each serotype by vaccine group.

6.2.3. Secondary Endpoint(s): Infant Participants (Stages 2 and 3)

6.2.3.1. GBS6 Serotype-Specific IgG GMCs Measured at Birth in Infant Participants

Endpoints: GBS6 serotype-specific IgG antibody concentrations.

- Analysis time point: At birth.

- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) populations for infant participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics and MMRM.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of participants with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented for each serotype, by maternal vaccine group.
- GMCs and associated 95% CI from the MMRM analysis specified in Section 6.3.4.1.

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical RCDCs for the at-birth time point will be generated separately for each serotype, by maternal vaccine group.

6.2.3.2. GBS6 Serotype-Specific OPA GMTs Measured at Birth in Infant Participants

Endpoints: GBS6 serotype-specific OPA antibody titers.

- Analysis time point: At birth.
- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) populations for infant participants (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of participants with valid assay data (n), GMTs, and associated 2-sided 95% CI will be presented for each serotype, by maternal vaccine group.

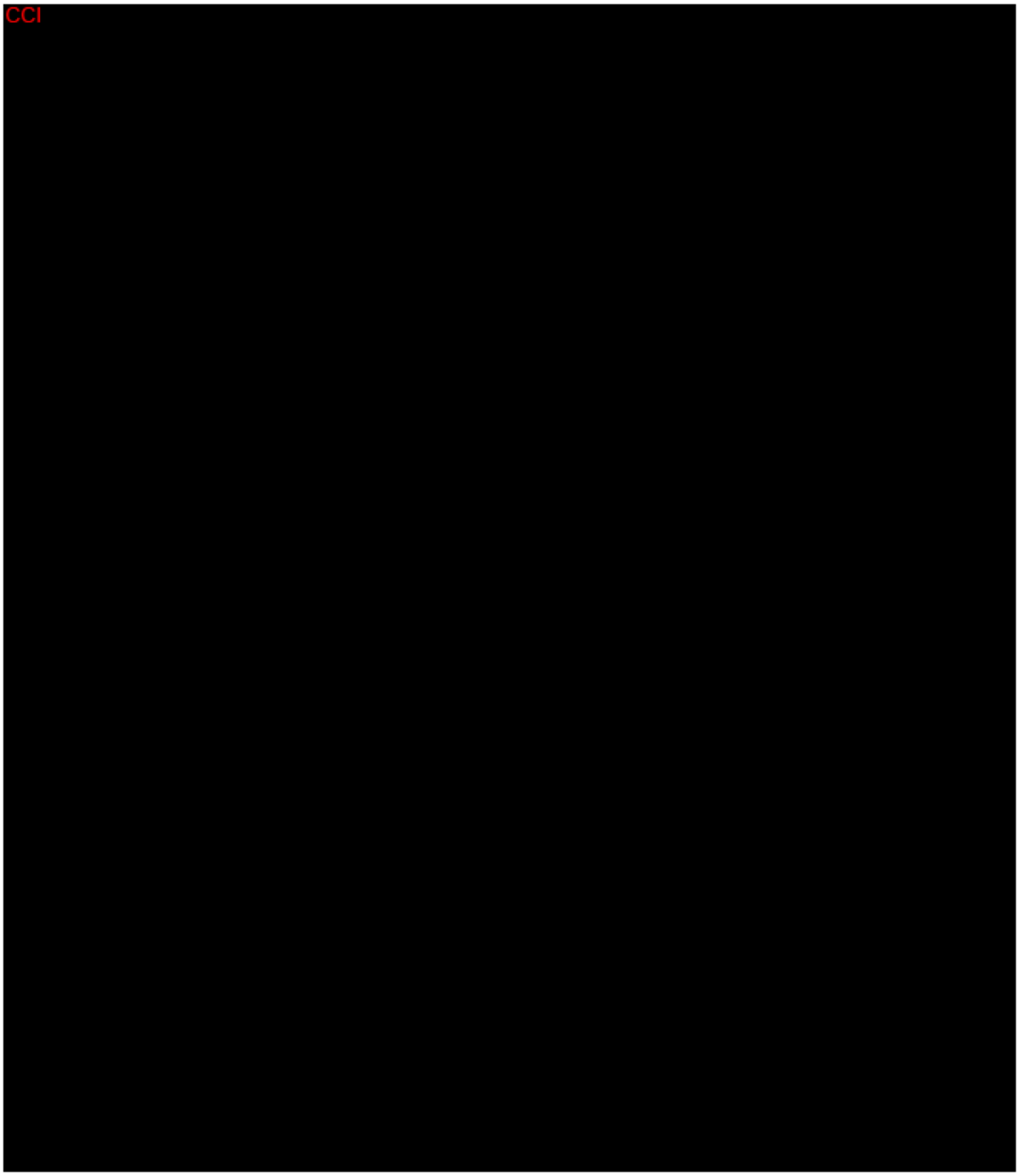
Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical RCDCs for the at-birth time point will be generated separately for each serotype, by maternal vaccine group.

6.3. Exploratory Endpoint(s)

6.3.1. Exploratory Endpoints: Nonpregnant Women Receiving the Primary Vaccination (Stage 1)

CCI



CCI

[redacted]

CCI

[redacted]

6.3.2. Exploratory Endpoints: Nonpregnant Women Receiving the Booster Vaccination (Stage 1)

CCI

[redacted]

CCI

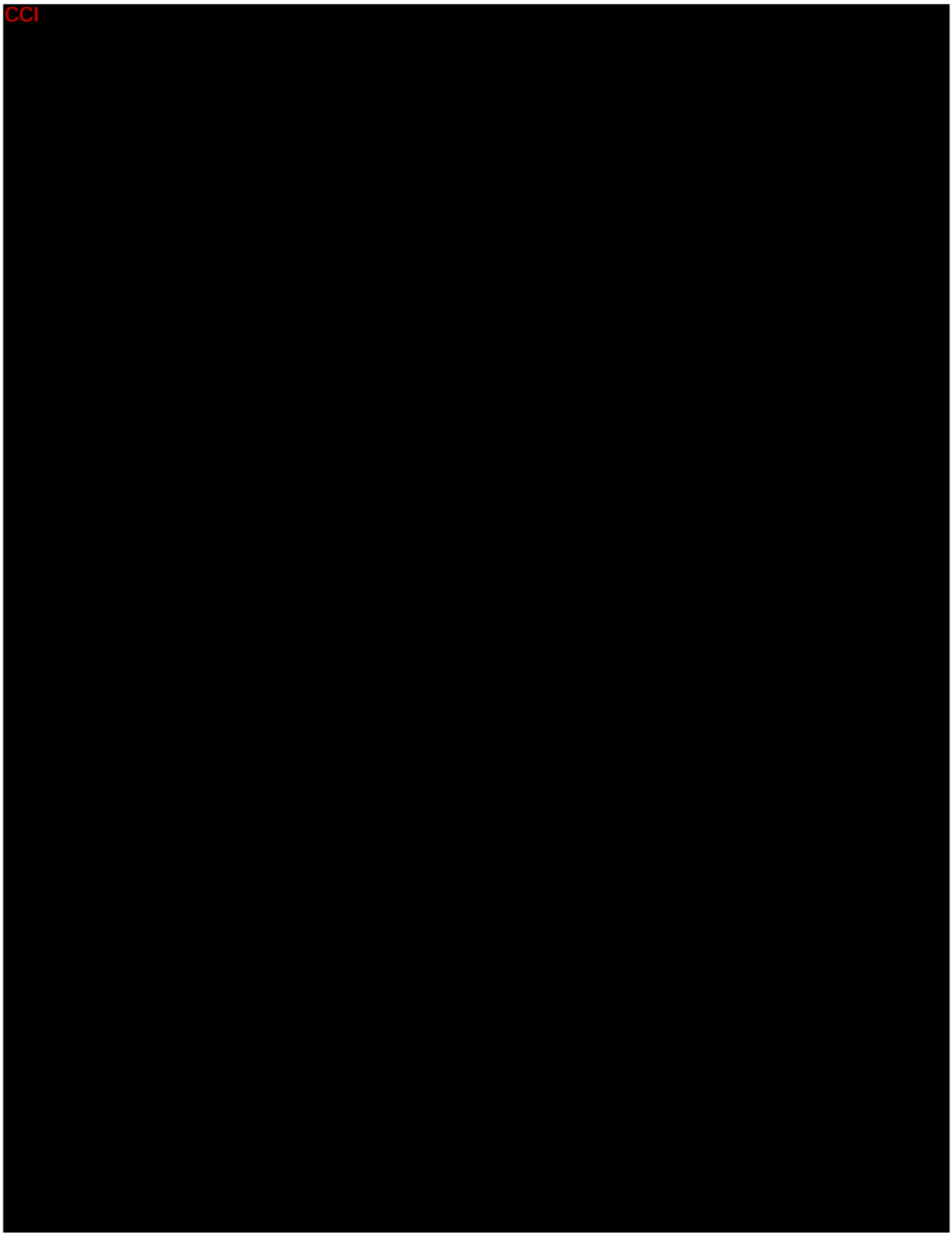
[redacted]

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

CCI

[redacted]

CCI



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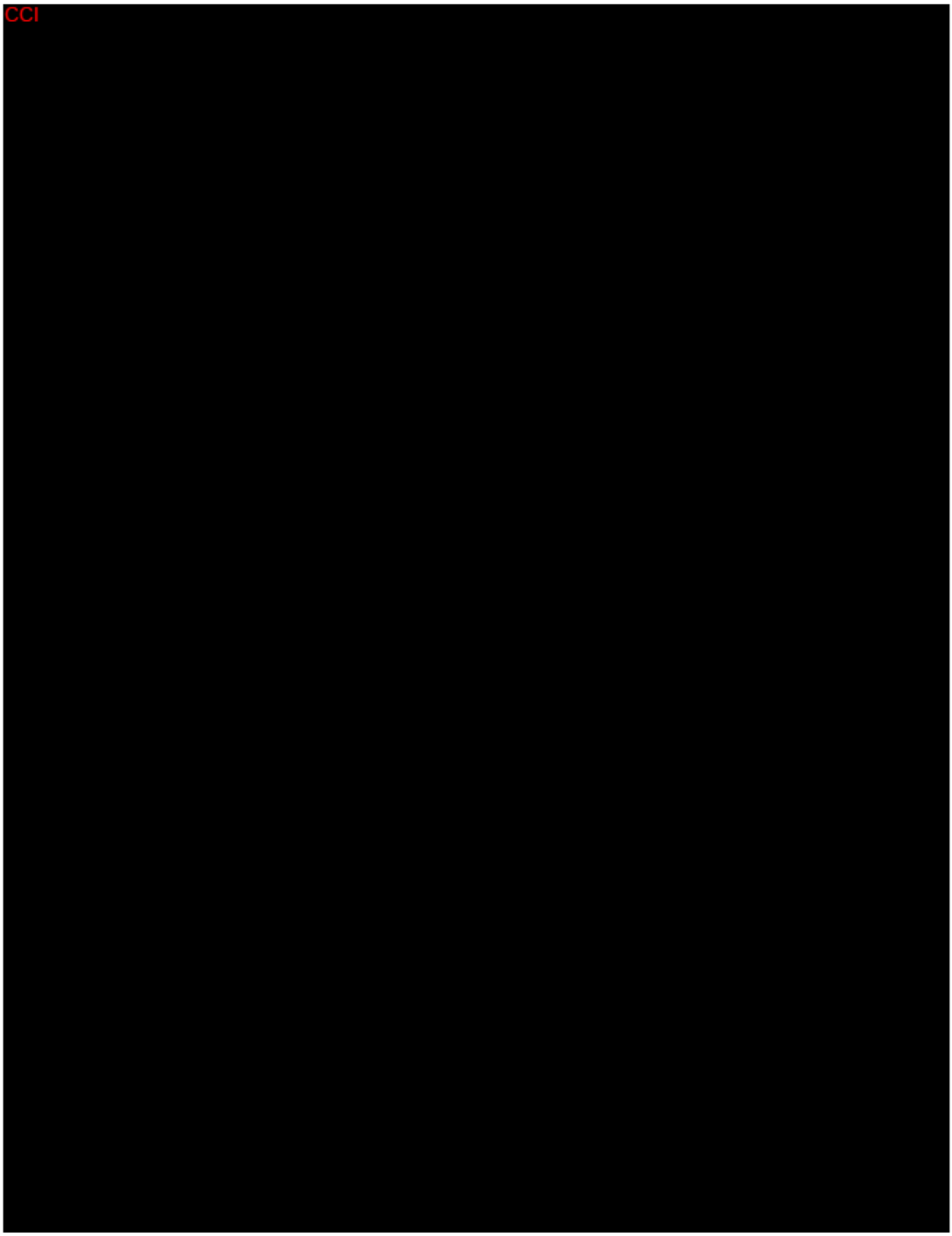

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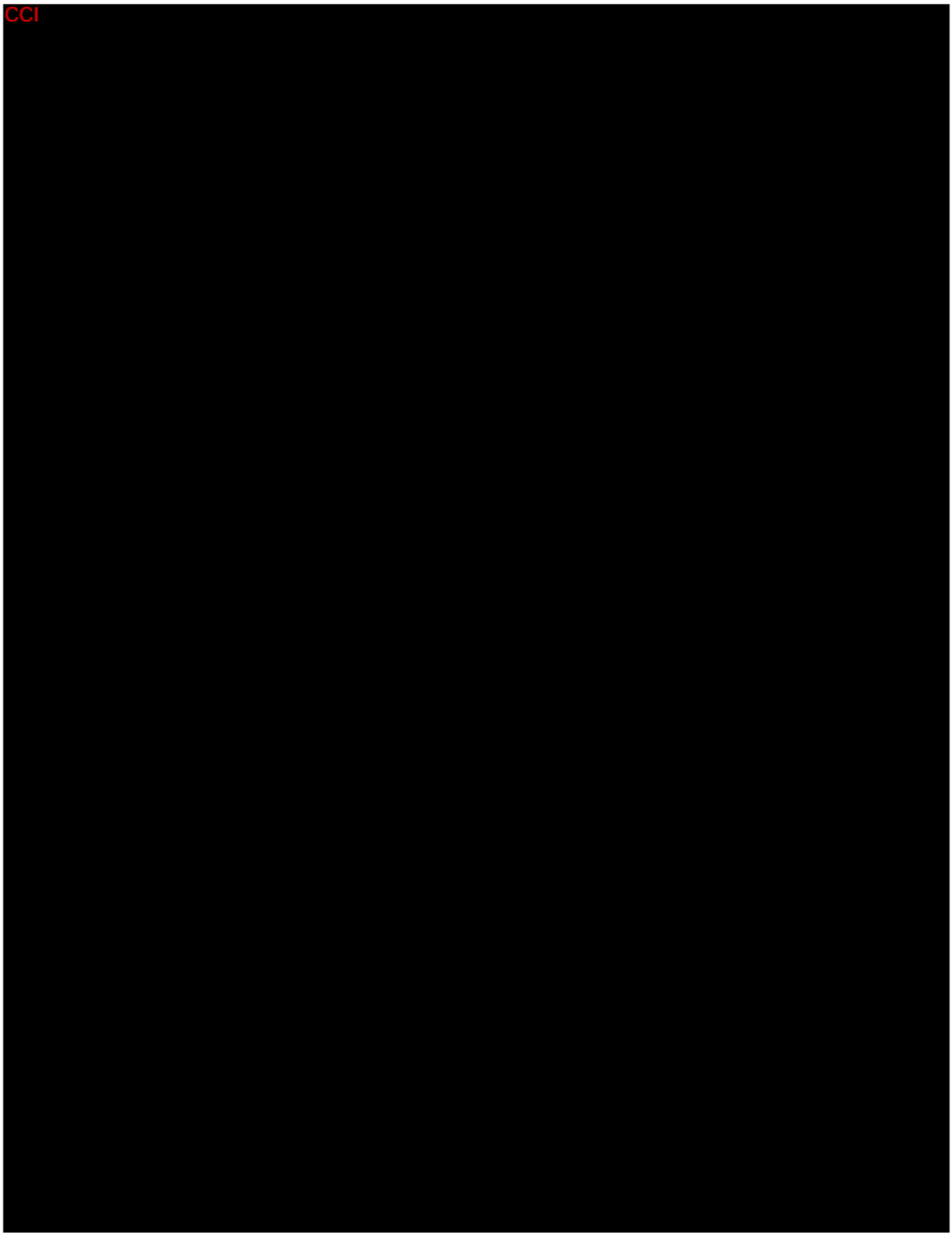

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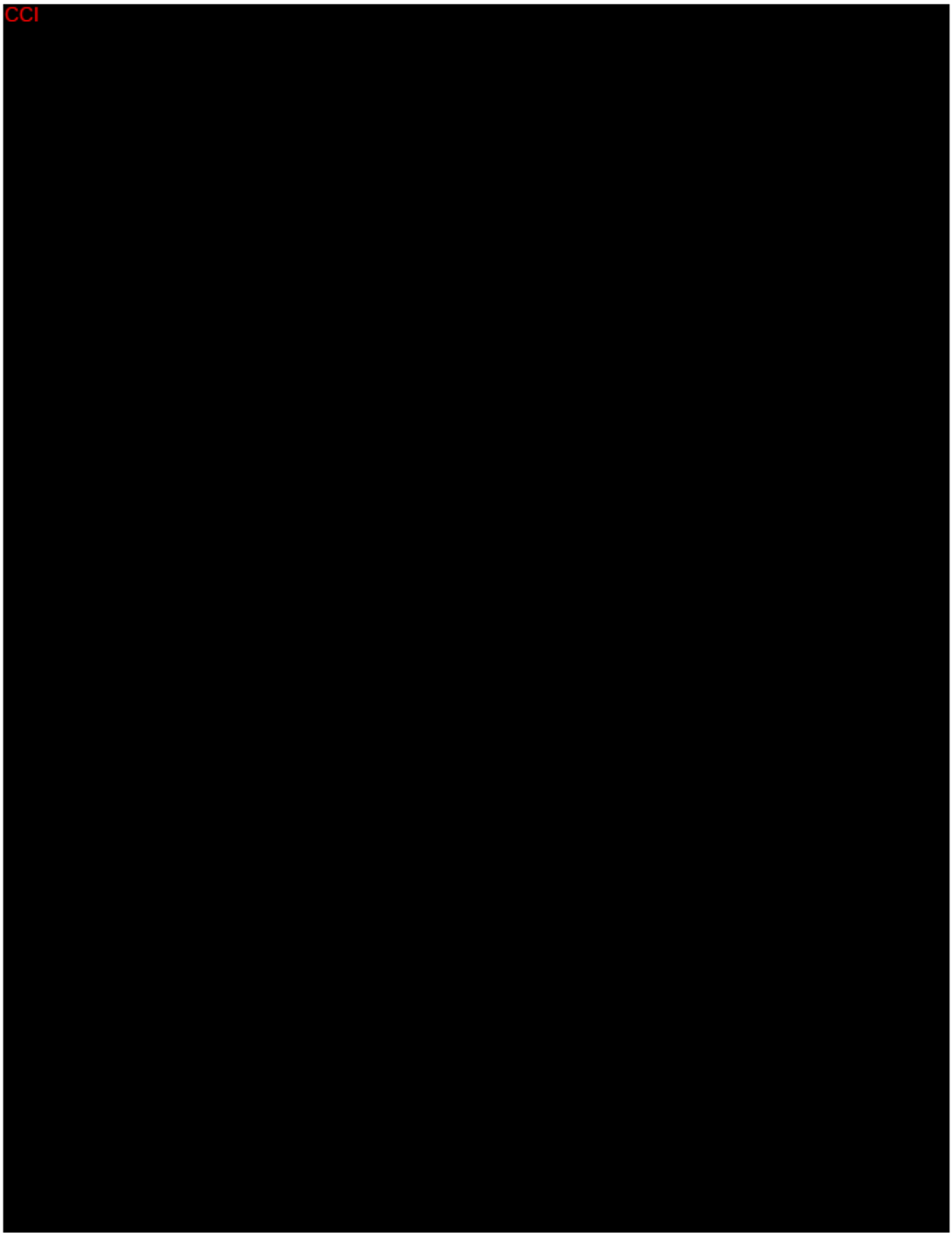


CCI

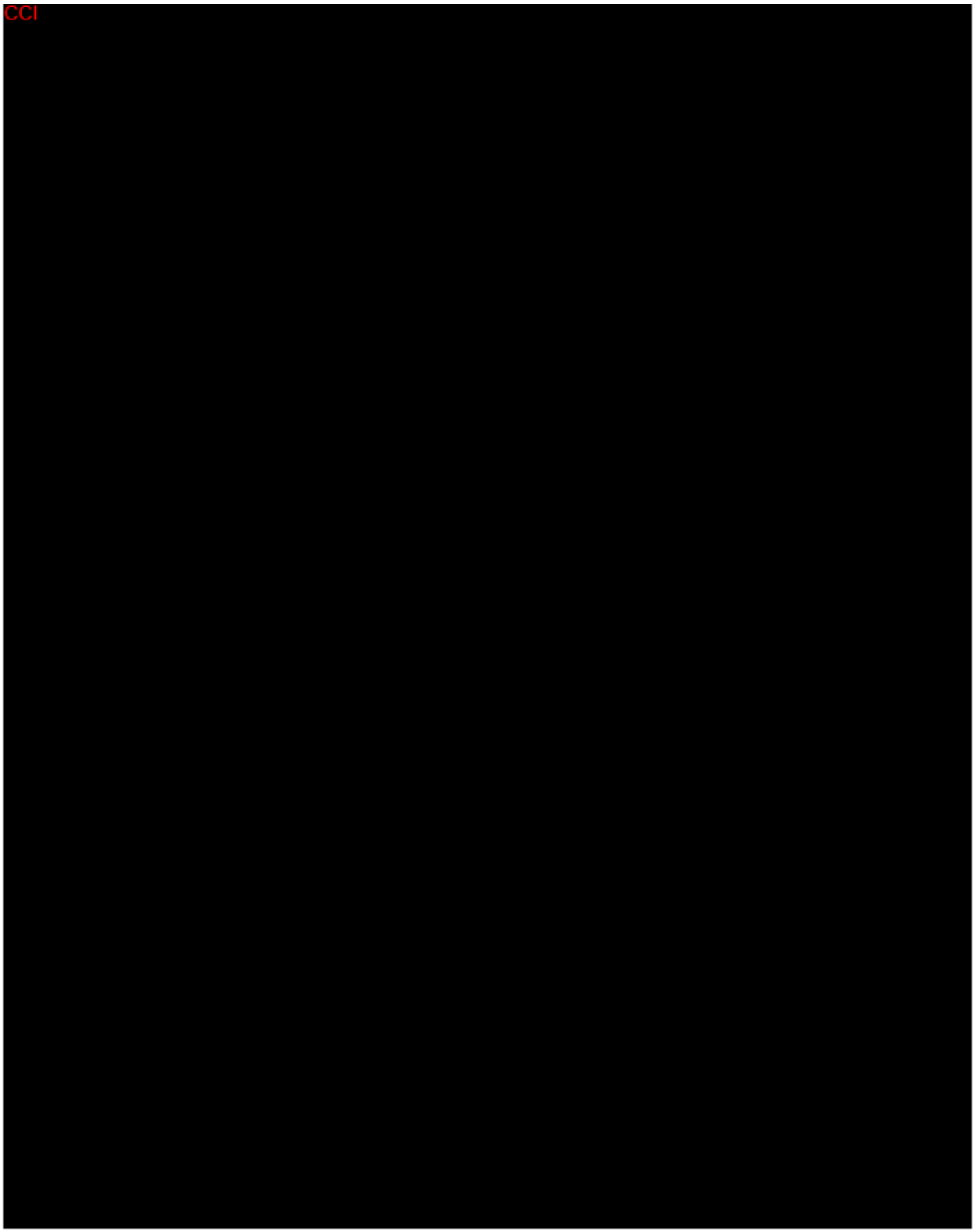
[redacted]

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

CCI

[redacted]

CCI



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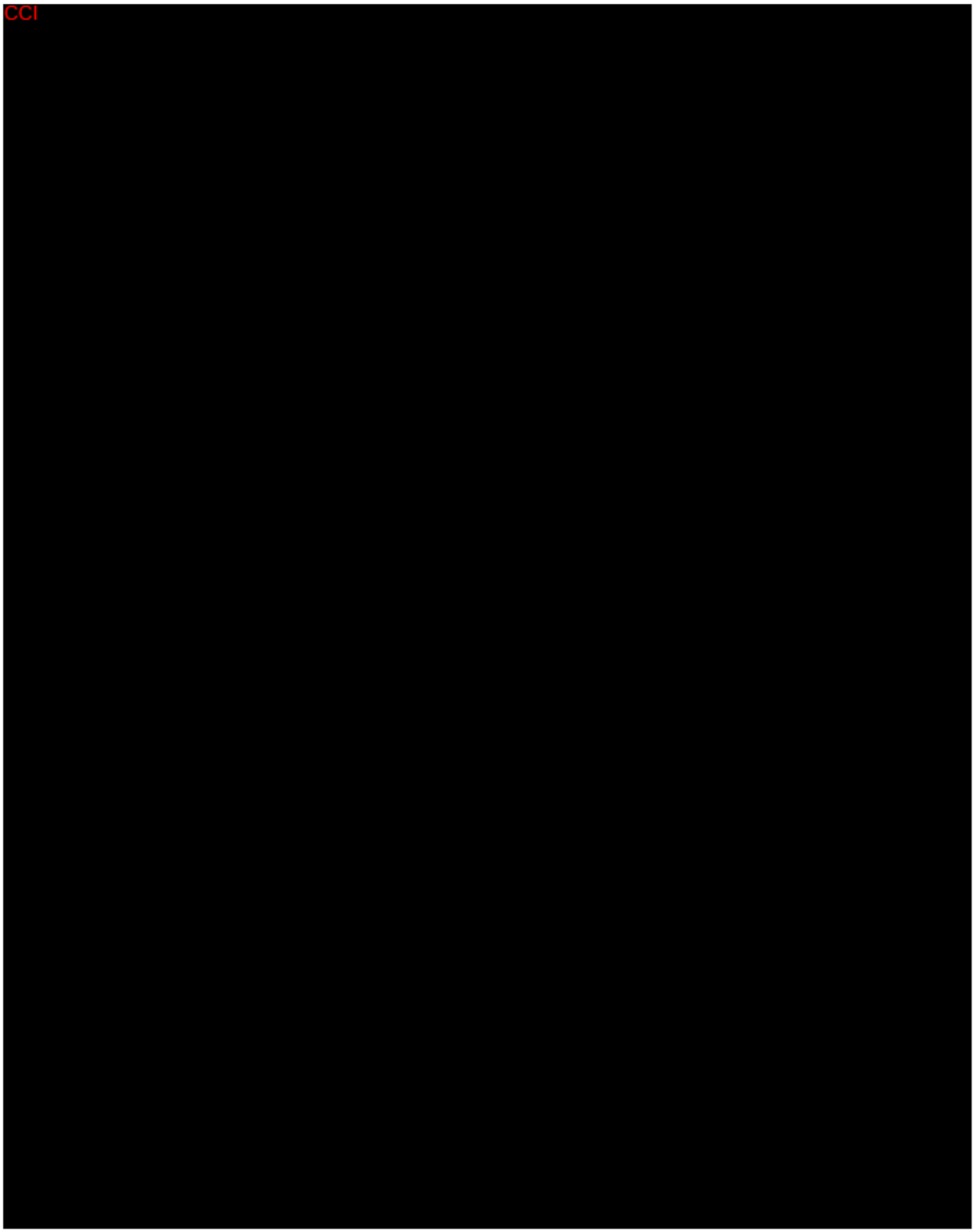
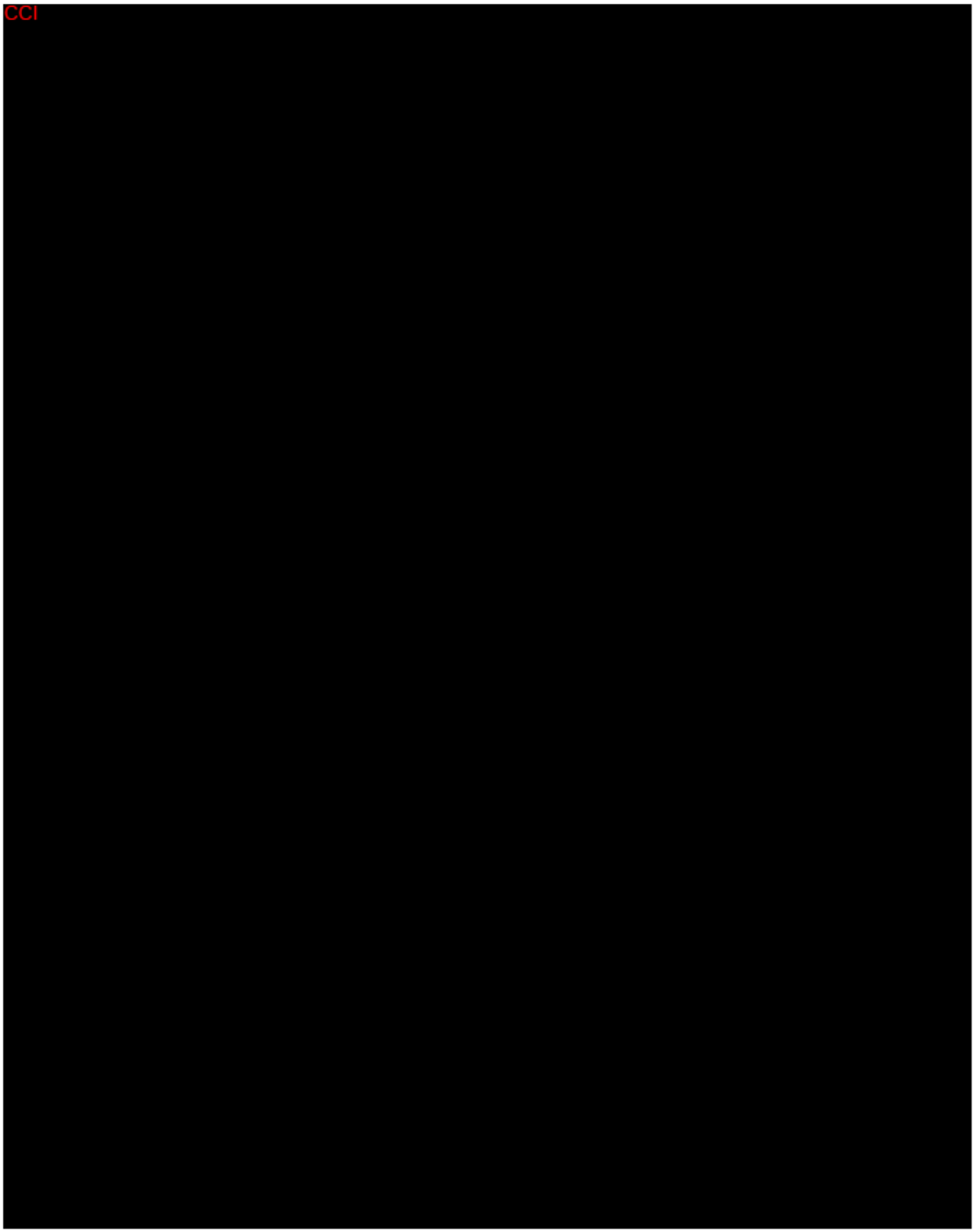
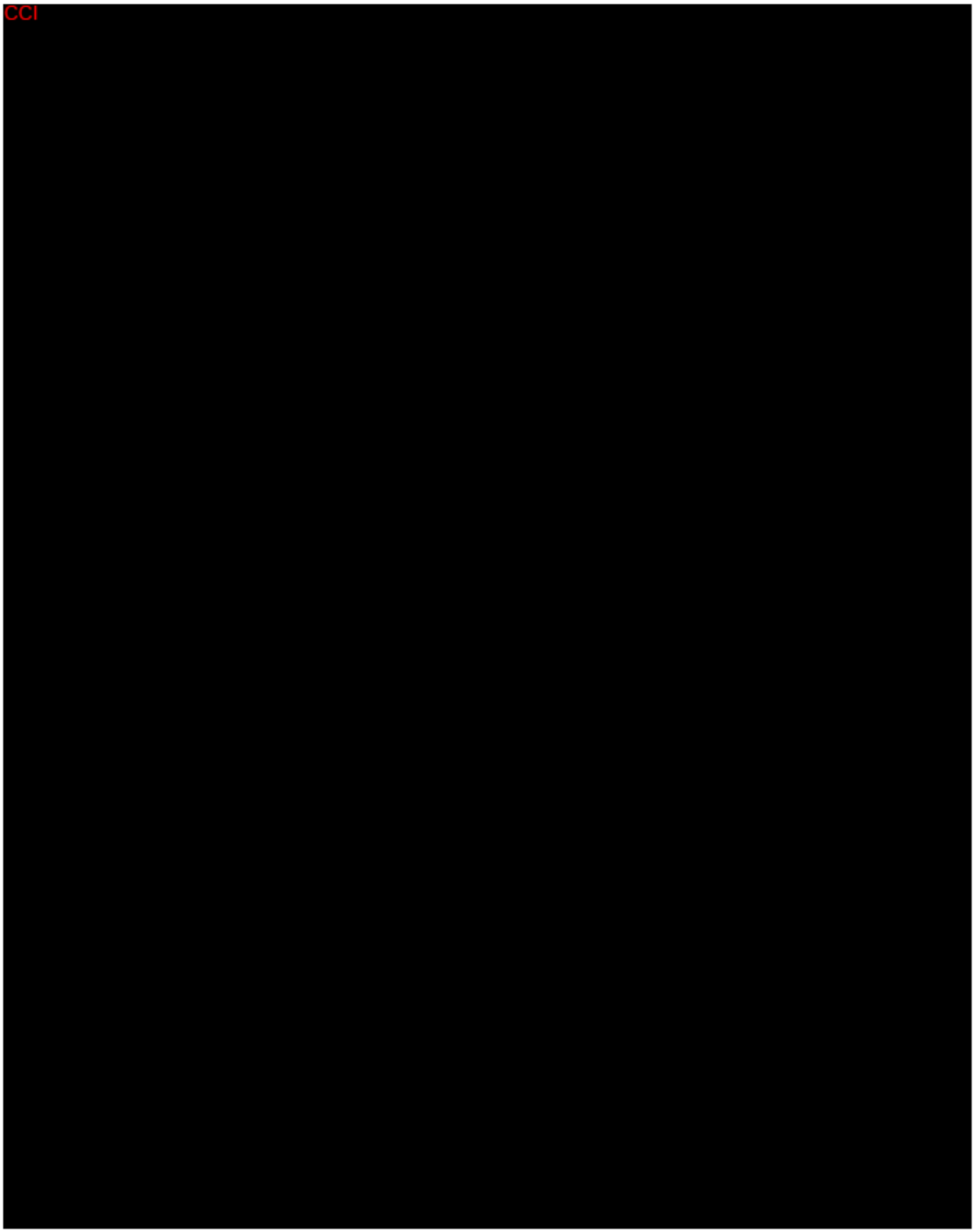


CCI



CCI



CCI

[redacted]

6.3.5. Exploratory Endpoints: Maternal and Infant Pairs (Stages 2 and 3)

CCI

[redacted]

6.4. Subset Analyses

CCI

[redacted]

CCI [redacted]

Table 9. Summary of Exploratory Subgroup Analyses for Maternal Participants (Stages 2 and 3)

Subgroup	Endpoints	Analysis Methodology	Analysis Time Points	Reporting Results
CCI [redacted]				

Table 10. Summary of Exploratory Subgroup Analyses for Infant Participants (Stages 2 and 3)

Subgroup	Endpoints	Analysis Methodology	Analysis Time Points	Reporting Results
CCI				

6.5. Other Analyses

CCI

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

6.6.1.1. Demographics and Medical History: Nonpregnant Women (Stage 1)

Descriptive summary statistics for demographic characteristics of the primary and booster vaccinations, as described in Section 3.4.1 (eg, age at vaccination), will be generated by vaccine group (3 vaccine groups for primary vaccination and 1 vaccine group for booster vaccination) and the total sample will be based on the safety population.

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

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

6.6.1.2. Demographics, Substance Use, Medical History, and Obstetric History: Maternal Participants (Stages 2 and 3)

Descriptive summary statistics for demographic characteristics, current alcohol and tobacco usage, medical history, and obstetric history, as described in Section 3.4.2, will be generated by vaccine group and the total sample will be based on the safety population.

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

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

6.6.1.3. Demographics and Feeding Information: Infant Participants (Stages 2 and 3)

Descriptive summary statistics for demographic characteristics and feeding information, as described in Section 3.4.3, will be generated by maternal vaccine group and the total sample will be based on the safety population.

Participant data listings for demography and other infant data will also be generated.

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. E-Diary Completion

For any given day, an e-diary will be transmitted and considered as complete if all expected data (the 3 local reactions, the 7 systemic reactions [including fever], and the use of antipyretics) are available. If any of the items in the e-diary are missing on a specific day, the e-diary will not be transmitted, and the e-diary data will be missing for all items on that day.

Partial completion of the e-diary card on any given day is not possible. The e-diary completion (or transmission) rate will be provided after each vaccination on Days 1 through 7. The denominator will be the total number of participants who received the vaccination, and the numerator will be the total number of participants with e-diary data transmitted on a given day. Additional e-diary compliance parameters for each vaccination will be derived as follows:

1. Presence or absence of each local reaction on each day (Days 1-7) after vaccination. E-diaries are completed for at least 1 day. The numerator is the number of participants who completed (transmitted) the e-diary on any day, and the denominator is the total number of participants who received a vaccination.

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

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

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

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

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

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

The number and proportion of participants with e-diary data not transmitted, transmitted by day (Days 1-7), and transmitted all days will be summarized by vaccine group (3 vaccine groups for primary vaccination and 1 vaccine group for booster vaccination) and the total sample. These summaries will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1) and maternal participants (Stages 2 and 3).

6.6.2.2. Participant Disposition

The number and proportion of randomized participants will be included in the participant disposition summary for nonpregnant women receiving the primary and booster vaccinations from Stage 1 and for maternal participants from Stages 2 and 3. For infant participants from Stages 2 and 3, number and proportion of enrolled participants will be displayed. In addition, participants who either completed each follow-up visit or withdrew before the follow-up visit, along with the reasons for withdrawal, will be tabulated by vaccine group or maternal vaccine group for infant participants. The reasons for withdrawal will be those as specified in the database. Additionally, participants who missed at least 1 study procedure but continued in the study for the safety follow-up will be summarized. Participant disposition tables will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3).

Participants excluded from the evaluable immunogenicity and mITT populations will also be summarized with reasons for exclusion. These summaries will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3).

The number and proportion of participants randomized (or assigned to the Stage 1 booster dose), vaccinated among nonpregnant women receiving the primary and booster vaccinations from Stage 1 and among maternal participants from Stages 2 and 3, and had blood drawn within or outside of the protocol-specified time frame will be tabulated by vaccine group or maternal vaccine group for infants and for the total sample. These summaries will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3).

Participant data listings of participants who withdrew during the study will be generated. Also, data listings for participants excluded from the evaluable and mITT populations will be generated separately. These listings will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3).

The protocol deviations listings will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3). In addition, participants who do not receive the vaccine as randomized will be listed separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1) and maternal participants (Stages 2 and 3).

6.6.3. Study Treatment Exposure

Not applicable.

6.6.4. Concomitant Medications and Nondrug Treatments

Data on nondrug treatments will not be collected in this study.

Nonstudy vaccines and medications taken after signing the ICD and until the end of the study will be categorized according to the WHO Drug Dictionary and summarized in accordance with the sponsor reporting standards. These will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3).

Antipyretic medication taken prior to vaccination by nonpregnant women receiving the primary and booster vaccinations (Stage 1) and maternal participants (Stages 2 and 3) will be summarized separately. Additionally, antibiotic medication taken by maternal participants (Stages 2 and 3) and infant participants (Stages 2 and 3) throughout the course of the study will be summarized separately.

6.7. Safety Summaries and Analyses

6.7.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of an investigational product and an AE or group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis. There will be no adjustment for multiple comparisons in the analyses.

AEs will be reported in accordance with the Pfizer reporting standards. For Tier 2 and Tier 3 events, the proportion of participants with AEs in each vaccine group will be presented. In addition, for Tier 2 AEs, 2-sided 95% CIs for the difference in observed proportions between each vaccine group and the placebo will be constructed. Tier 3 events will be summarized as part of the overall AE summary.

AEs, MAEs, and SAEs occurring after signing the ICD and prior to vaccination will be summarized separately for nonpregnant women receiving the primary and booster vaccinations from Stage 1 and for maternal participants from Stages 2 and 3.

Listings of participants reporting any AE will be generated for all participants.

Additionally, immediate AEs will be generated for nonpregnant women receiving the primary and booster vaccinations from Stage 1 and for maternal participants from Stages 2 and 3.

All summaries and listings for the AEs will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3). Additionally, suspected or confirmed GBS infections for infant participants (Stages 2 and 3) will be summarized by EOD and LOD as defined in Section 3.6.1.

6.7.2. Reactogenicity Data

The derived endpoints (Section 3.6.2) for each local reaction, systemic event, and use of antipyretic/pain medication will be summarized.

Additionally, for the baseline assessment of systemic events collected on Day 1 for maternal participants (Stages 2 and 3), the number and percentage of participants with individual systemic events along with the corresponding 2-sided 95% CIs will be displayed separately, by vaccine group.

The number and percentage of participants with individual local reactions and any local reaction will be summarized on each of Days 1 through 7 separately. Two (2)-sided 95% CIs will also be displayed. A similar set of outputs may be produced combining reactions that are moderate or severe in grade. Similar analysis will be repeated for each systemic event and any systemic event.

For the maximum duration of local reactions, systemic events, and use of antipyretic/pain medication, descriptive summary statistics will be provided separately.

For the onset (day) of local reactions, systemic events, and use of antipyretic/pain medication, descriptive summary statistics will be provided separately.

The maximum reported diameters for redness and swelling will be summarized using descriptive statistics, by vaccine group.

A participant data listing will be provided for all reactogenicity data and for participants experiencing severe redness or swelling.

All summaries and listings for the reactogenicity data will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1) and maternal participants (Stages 2 and 3).

6.7.3. Laboratory Data

Descriptive summaries for laboratory abnormalities at 2 weeks after vaccination, as described in Section 3.6.3, will be provided by vaccine group. Also, separate listings for participants with abnormal laboratory results at 2 weeks after vaccination and participants retested for abnormal laboratory results at screening or 2 weeks after vaccination will be generated. These summaries and listings will be generated only for maternal participants (Stage 2 sentinel cohort).

6.7.4. Physical Examinations, Including Vital Signs

Descriptive summaries based on the safety population will be provided in accordance with the Pfizer reporting standards and listings may be generated. All summaries and listings for these data will be generated separately for nonpregnant women receiving the primary and

booster vaccinations (Stage 1), maternal participants (Stages 2 and 3), and infant participants (Stages 2 and 3).

6.7.5. Obstetric Examinations and Pregnancy Outcomes

Descriptive summaries and data listings will be generated for the obstetric examination findings and pregnancy outcomes. These summaries and listings will be generated only for maternal participants (Stages 2 and 3).

7. ANALYSES TIMING

7.1. Introduction

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded study. Analyses results described below will be provided to the appropriate sponsor personnel as needed to make program-related decisions. In addition to these, unblinded safety data reviews by an external data monitoring committee (E-DMC) are scheduled to occur approximately twice a year. Additional details can be found in the E-DMC charter.

An internal review committee (IRC) will review the 1-month postvaccination safety data from Stage 1 primary vaccination and the 1-month safety and immunogenicity data of the various GBS6 formulations from the first-in-human (FIH) Phase 1/2 study before progression into Stage 2. Additionally, the IRC will review unblinded 14-day safety data for maternal participants from each sentinel cohort of Stage 2 prior to determining if expanded enrollment may begin at that dose level and whether enrollment into the next higher dose sentinel cohort may begin. The IRC will meet on an ad hoc and timely basis to review safety data for maternal participants from Stage 2 if a stopping rule is triggered and make recommendations for the study. The IRC will also select the GBS6 final dose and formulation to take into Stage 3 and further development. Details on timing, responsibility, and reporting will be included in the IRC charter and stopping rule plan.

7.2. Interim Analyses and Summaries

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 the Stage 1 primary vaccination 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 E-DMC will review the available unblinded data, and the IRC, in consultation with the E-DMC, will make the recommendations regarding the study proceeding to Stage 2.

The second interim analysis will be performed when postdelivery/postbirth safety and immunogenicity data from all sentinel-cohort maternal participants and their infants in Stage 2 are available. Safety and immunogenicity data from all sentinel-cohort maternal participants and their infants in Stage 2 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.

The third interim analysis will be performed when the delivery/birth safety and immunogenicity data from all maternal participants and their infants in Stage 2 are available. All available safety and immunogenicity data from all Stage 2 (maternal and infant) 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.

The fourth interim analysis will be performed when delivery/birth safety and immunogenicity data from all maternal participants and their infants in Stage 3 are available. All available safety and immunogenicity data from all Stage 3 (maternal and infant) 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.

No multiplicity adjustments will be applied for these assessments.

Sponsor study team members will be unblinded to the vaccine assigned/received by participants within a stage at the time of the interim analysis. The only exception to this is the second interim analysis, where the study team will only be unblinded for the sentinel-cohort data and will remain blinded for all expanded cohorts. Major protocol violations will be identified and documented in the study data handling memo prior to the unblinded 1-month safety analysis. Laboratory personnel performing the immunologic assays will remain blinded to vaccine assigned/received throughout the study.

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

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

8. REFERENCES

1. Sheffield JS, Munoz FM, Beigi RH, et al. Research on vaccines during pregnancy: reference values for vital signs and laboratory assessments. Vaccine 2013;31(40):4264-73.

2. Newcombe RG. Two-sided intervals for the single proportion: comparison of seven methods. Stat Med 1998;17(8):857-72.

3. Collett D. Modeling binary data. 1st ed. London: Chapman & Hall; 1991.

4. Chan ISF and Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55(4):1202-9.

5. Siddiqui O, Hung HM, O'Neill R. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat 2009;19(2):227-46.

9. APPENDICES

Table 11. Summary of Immunogenicity and Colonization Data Analyses (Excluding Subgroup)

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
1 (Nonpregnant women)	Evaluable immunogenicity population for nonpregnant women	Blood	GBS6 serotype-specific IgG, primary vaccination	GMCs and CCI from the primary vaccination Day 1 to each postvaccination time point, along with respective 95% CIs	Day 1 (before the primary vaccination) and 2 weeks and 1 month after the primary vaccination	Continuous
				Proportion of participants achieving a defined IgG level (eg, 1.0 µg/mL) and corresponding 95% CIs	Day 1 (before vaccination) and 2 weeks and 1 month after the primary vaccination	Binary
				RCDCs	1 Month after the primary vaccination	Continuous
				Antibody response curves	Day 1 (before the primary vaccination) and 2 weeks and 1 month after the primary vaccination	Continuous
				GMCs at each analysis time point based on the mITT population, if the proportion of participants in the mITT population differs from that of the evaluable immunogenicity population by at least 10%	Day 1 (before the primary vaccination) and 2 weeks and 1 month after the primary vaccination	Continuous
			GBS6 serotype-specific IgG, booster vaccination	GMCs and CCI of the booster vaccination from before to each postvaccination time point, along with respective 95% CIs	Prebooster Day 1 (before the booster vaccination) and 1 month, 3 months, and 6 months after the booster vaccination	Continuous

Table 11. Summary of Immunogenicity and Colonization Data Analyses (Excluding Subgroup)

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
				Proportion of participants achieving a defined IgG level (eg, 1.0 µg/mL) and corresponding 95% CIs	Prebooster Day 1 (before the booster vaccination) and 1 month, 3 months, and 6 months after the booster vaccination	Binary
				RCDCs	Prebooster Day 1 (before the booster vaccination) and 1 month, 3 months, and 6 months after the booster vaccination	Continuous
				Antibody response curves	Prebooster Day 1 (before the booster vaccination) and 1 month, 3 months, and 6 months after the booster vaccination	Continuous
	Randomized nonpregnant women	Rectal and vaginal swabs	GBS6 serotype-specific colonization status following primary vaccination	Proportion of participants with positive results and corresponding 95% CIs by serotype	Day 1 (before the primary vaccination) and 1 month after the primary vaccination	Binary
2 And 3 separately (maternal participants)	Evaluable immunogenicity population for maternal participants	Blood	GBS6 serotype-specific IgG	GMCs and CCI from Day 1 to each postvaccination time point, along with respective 95% CIs	Day 1, 2 weeks and 1 month after vaccination, at delivery, and 6 weeks and 12 months after delivery	Continuous
				Proportion of participants achieving a defined IgG level (eg, 1.0 µg/mL) and corresponding 95% CIs	Day 1, 2 weeks and 1 month after vaccination, at delivery, and 6 weeks and 12 months after delivery	Binary

Table 11. Summary of Immunogenicity and Colonization Data Analyses (Excluding Subgroup)

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
				RCDCs	1 Month after vaccination and at delivery	Continuous
				Antibody response curves	Day 1, 2 weeks and 1 month after vaccination, at delivery, and 6 weeks and 12 months after delivery	Continuous
				MMRM to assess the effects of regressors/covariates, such as vaccine group, visit (blood-sampling time point), baseline GBS6 serotype-specific IgG antibody level, age at vaccination (years), and Day 1 serotype-specific colonization status (positive or negative), on the associated GBS6 serotype-specific postvaccination IgG antibody levels	Day 1, 2 weeks and 1 month after vaccination, at delivery, and 6 weeks and 12 months after delivery	Continuous
			CCI [redacted]			

Table 11. Summary of Immunogenicity and Colonization Data Analyses (Excluding Subgroup)

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
			CCI			
	CCI					
2 And 3 separately (infant participants)	Evaluable immunogenicity population for infant participants	Blood	GBS6 serotype-specific IgG	GMCs and CCI from birth through 14 weeks of age along with respective 95% CIs	At birth, 6 weeks, and 14 weeks of age	Continuous
				Proportion of participants achieving a defined IgG level (eg, 1.0 µg/mL) and corresponding 95% CIs	At birth, 6 weeks, and 14 weeks of age	Binary
				RCDCs	At birth	Continuous
				Antibody response curves	At birth, 6 weeks, and 14 weeks of age	Continuous

Table 11. Summary of Immunogenicity and Colonization Data Analyses (Excluding Subgroup)

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
				MMRM to assess the effects of regressors/covariates, such as the maternal vaccine group, visit (blood sampling time point), at-birth GBS6 serotype-specific IgG antibody level, sex (male, female, or undifferentiated), delivery outcome (preterm vs full-term), CCI [redacted], on the associated GBS6 serotype-specific postvaccination IgG antibody levels	At birth, 6 weeks, and 14 weeks of age	Continuous
			GBS6 serotype-specific OPA	GMTs at birth along with respective 95% CIs	At birth	Continuous
				RCDCs	At birth	Continuous
				Antibody response curves	At birth	Continuous
			CCI [redacted]			
				CCI [redacted]		
				Antibody response curves	At birth	Continuous
			GBS6 serotype-specific IgG and CCI [redacted] (Stage 2 only)	GMRs for CCI [redacted] /IgG along with respective 95% CIs	At birth	Continuous

Table 11. Summary of Immunogenicity and Colonization Data Analyses (Excluding Subgroup)

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
	CCI					

Table 11. Summary of Immunogenicity and Colonization Data Analyses (Excluding Subgroup)

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
	CCI					
2 And 3 separately (maternal and infant pairs)	Evaluable immunogenicity population for maternal and infant pairs	Blood	CCI			
			CCI			

Document Approval Record

Document Name:	C1091002 Statistical Analysis Plan V5 Clean Copy, 02Feb2023
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	01-Feb-2023 20:07:55	Final Approval