Potential for Maternally Administered Vaccine for Infant Group B Streptococcus

The protocols (clinical and seroepidemiology studies) and the statistical analysis plan have been provided by the authors to give readers additional information about their work.

This supplement contains the following items:

1. Seroepidemiology protocol

2. Original protocol, final protocol containing summary of changes

3. Original statistical analysis plan, final statistical analysis plan containing summary of changes

Investigating for immunological correlates of protection against invasive Group B *streptococcus* disease in infants less than 90 days of age.

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Abbreviations

CHBH	Chris Hani Baragwanath Hospital
RMPRU	Respiratory and Meningeal Pathogens Research Unit
BMH	Bheki Mlangeni Hospital
CDC	Centers for Disease Control and Prevention
CHBAH	Chris Hani Baragwanath Academic Hospital
CLSI	Clinical and Laboratory Standards Institute
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CPS	Capsular polysaccharide
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
EC	Ethics Committee
EDC	Electronic Data Capture
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EOD	Early onset disease
FDA	Food and Drug Administration
FSFV	First Subject First Visit
GBS	Group B Streptococcus/Streptococcus agalactiae
GBS-CV	Group B Streptococcus protein-polysaccharide conjugate vaccine
GBS-TCV	Group B Streptococcus Tri-valent protein-polysaccharide conjugate vaccine
GCP	Good Clinical Practice
GM	Geometric Mean
GPP	Good Pharmaco-epidemiology Practice
GSK	Glaxo Smith Kline
HREC	Human Research Ethics Committee
IAP	Intra-partum antibiotic Prophylaxis
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IRB	Institutional Review Board
LNC	Lillian Ngoyi Clinic
LOD	Late onset disease
MIA	Multiplex Immunological Assay
NHLS	National Health Laboratory Service
OPK	Opsonophagocytic killing
PCR	Polymerase Chain Reaction
RMMCH	Rahima Moosa Mother and Child Hospital
RMPRU	Respiratory and Meningeal Pathogens Research Unit
SBA	Serum bactericidal assays
SDA	Source Document Assessment

1. Introduction and Background

Streptococcus agalactiae or Group B *Streptococcus* (GBS) is a leading cause of neonatal sepsis in developed and developing countries (1,2). In the year 2015, an estimated 21.7 million births occurred in women who were colonized with GBS in the rectum and/or vagina; a major risk factor for their offspring to develop invasive GBS disease and almost a pre-requisite for disease occurring within 6 days of birth (i.e. early-onset invasive GBS disease; GBS-EOD). Furthermore, there were an estimated 319,000 invasive GBS disease cases in infants under 3 months of age in 2015, 90,000 (uncertainty range [UR] 36 000-169 000) of which were fatal and a further 10,000 (UR 3 000- 27 000) of whom developed neurological disabilities primarily secondary to GBS meningitis (1,2).

Globally, an estimated 18% (95% confidence interval [CI], 17%- 19%) of women have recto-vaginal GBS at the time of delivery, with the highest prevalence (25.3%, 95%CI, 22.1-28.5) in Southern Africa(3). The majority of invasive GBS disease in children occurs within 90 days of birth, which is traditionally stratified as GBS-EOD and late-onset disease (GBS-LOD; i.e. illness onset between 7 and ≤89 days of age). The global incidence (per 1,000 live births) of invasive GBS disease is estimated at 0.49 (95%CI, 0.43-0.56), with the highest incidence in Southern Africa (2.00, 95%CI, 0.74-3.26)(1). In Soweto, South Africa, the overall incidence of invasive GBS disease between 2005 and 2014 was 2.59 (95%CI, 1.06-1.30), with incidence of GBS-EOD at 1.41 (95%CI, 1.28-1.55) and GBS-LOD at 1.18 (95% CI; 1.06-1.30)(4). Associated case fatality risk of invasive GBS disease vary by region from 7% in Europe to 22% in Africa(2).

In 2015, there were an estimated 2.65 million (UR 2.08-3.79 million) stillbirths globally, 35.6% (943 900) of which occurred in sub-Saharan Africa(5). The annual number of stillbirths in 2015 was similar to the total number of neonatal deaths (2.7 million)(6). A conservative estimate is that invasive GBS disease of the foetus causes 4-5% of stillbirths, approximating 57,000 stillbirths in 2015 (7). The pathogenesis of GBS-associated stillbirth likely follows ascending infection of the foetus in women with recto-vaginal GBS colonization, which could cause chorio-amnionitis (infection of the placenta), or direct infection of the amniotic fluid that is

subsequently aspirated by the foetus. Notably, intra-amniotic infection could occur even in the presence of a macroscopically intact amniotic sac, by invasion through micro-tears of the membranes. GBS associated stillbirths possibly represents a continuum in spectrum of GBS-EOD, with *in utero* invasive GBS infection in the foetus presenting either as a stillbirth or the newborn being symptomatic at the time of birth, or very soon thereafter (i.e. GBS-EOD). This possibility is supported by 80-90% of GBS-EOD being diagnosed within 24 hours of birth; and very commonly in our own setting based on a blood culture that is taken from a newborn with signs of infection at the time of birth.

The introduction of screening for maternal recto-vaginal GBS colonization, with subsequent treatment of colonized women with intrapartum antibiotic prophylaxis (IAP) at least 2-4 hours prior to delivery, has resulted in >80% reduction in the incidence of GBS-EOD in high-income settings where such interventions have been implemented (8). The residual burden of GBS-EOD in these countries, however, remained similar to the incidence of GBS-LOD, which is not preventable by IAP. Implementation of a screening-based IAP strategy in low-middle income settings is unlikely to succeed due to logistical constraints such as difficulty in tracing colonized women prior to onset of labour, limited access to required intravenous antibiotics, and women needing to present 2-4 hours prior to delivery. Furthermore, there are other resource constraints, including availability of laboratory diagnostic facilities and monetary (9). Also, a screening-based IAP strategy results in almost 30-40% of pregnant women in high-income settings receiving antibiotics during labour, which could theoretically give rise to antimicrobial resistance by other colonizing bacteria in the mother and transmission thereof to their offspring, as well as impact on the newborn microbiome. Aberrations of the newborn microbiome are increasingly being associated with adverse infant outcomes, including possibly increased susceptibility to infections and allergies, as well as abnormal growth (9).

The above challenges in reducing rates of GBS invasive disease, disabilities and death, have encouraged research and development of GBS vaccines targeted at pregnant women. Such vaccines could protect the mother herself from GBS disease, as well as their infants. Protection of the infants is likely to be mainly mediated through increased transplacental acquisition of protective antibody from the mother,

in addition to which maternal vaccination could also reduce recto-vaginal GBS acquisition during pregnancy in the women, which could further reduce the risk of GBS-EOD and possibly GBS-associated adverse birth outcomes such as stillbirths and GBS-associated preterm labour.

Research on developing a GBS vaccine targeted at pregnant women date back to the 1980s as recently reviewed(10). Between 2010 and 2012, a tri-valent (serotypes Ia, Ib & III) GBS polysaccharide-protein conjugate vaccine underwent phase 1 and 2 studies for safety, dose selection and immunogenicity in non-pregnant and pregnant participants(11,12). These studies demonstrated acceptable safety profiles and immunological responses in vaccine recipients. More recently, a 6-valent (serotypes Ia, Ib, II, III, IV & V) GBS conjugate vaccine has entered into phase I studies in healthy men and non-pregnant women, with studies in pregnant women planned to be initiated in 2018/9. (HREC reference 180701). The selection of the 6 serotypes (of 10 known GBS serotypes) in the hexa-valent vaccine being developed was premised on epidemiological data indicating that 99% of all invasive GBS disease is caused by these serotypes; including approximately 78% due to serotypes Ia and III alone(13). Research is also underway on a GBS common protein-antigen vaccine, based on a fusion of highly immunogenic protein domains from two surface proteins of GBS (N-terminals of AlphaC and Rib, GBS-NN)(14).

In addition to the residual burden of GBS-EOD and unchanged incidence of GBS-LOD in countries where universal screening and IAP has been implemented, GBS has also emerged as the leading cause of bacterial meningitis in children <18 years of age in the USA(15) and elsewhere(16). Nevertheless, the current incidence of culture-confirmed invasive GBS disease in such countries, militates against undertaking a vaccine efficacy study in pregnant women to measure for protection against infant invasive GBS disease, due to what would be an unrealistically high sample size (>100,000 pregnant women). Even in settings with an incidence of invasive GBS disease between 1.5-2.0 per 1,000 live births; approximately 40,000-60,000 pregnant women would need to be enrolled to demonstrate 80% protection against vaccine-serotype invasive GBS disease in their infants as the outcome (17). This too would be too large a number of pregnant women to enroll, and is further compounded by the limited number of places globally that have the infrastructure to

undertake such a study and where the incidence of invasive GBS disease is in this range.

An alternate strategy for licensure of a GBS vaccine in pregnant women could be to demonstrate safety in approximately 3,000-4,500 pregnant women, and measure immunogenicity of the vaccine benchmarked against an established correlate of protection against invasive GBS disease in their infants. This pathway of vaccine licensure, i.e. safety determination coupled with immunogenicity benchmarked against correlate of protection derived from natural immunogenicity studies, has been the basis for licensure of meningococcal vaccines(18,19). Also new formulations of pneumococcal conjugate vaccine (PCV) are licensed based on safety, and immunogenicity that is benchmarked against putative correlate of protection across all serotypes that was imputed from initial vaccine-efficacy and immunogenicity studies(20).

Following early observations by Baker et al(21,22) demonstrating an association between maternal serotype-specific capsular antibody and risk of invasive GBS disease from homotypic serotypes, a number of subsequent studies have illustrated similar observations as reviewed by Dangor et al. (23). Some of the studies have proposed serotype-specific capsular antibody thresholds predictive of reduced risk of infant invasive GBS disease (i.e. correlate of protection) (23). Differences in study-design, age-range of invasive-disease cases, antibody assay methods and a lack of standardized reference serum between assays, however, has prevented establishment of a universally accepted correlate of protection. Furthermore, correlates of protection have only been proposed for the most common invasive-disease causing serotypes (Ia, III and V), and vary between 3 to 10-fold in the proposed threshold across studies. Another unresolved issue is whether a correlate of protection for infant invasive GBS disease should be established in relation to the maternal (as has been mainly done) or infant antibody levels. This is pertinent due to the multiplicity of factors that could influence transplacental antibody transfer, including differences between populations. In a study by Lin et. al., the threshold of maternal and infant serum IgG antibodies associated with 90% reduced risk of invasive GBS disease varied up to two-fold for serotype III (10 µg/ml for maternal vs.

5.0 µg/ml for cord-blood IgG levels), but less so for serotype Ia (5.0 µg/ml vs. 4.0 µg/ml in infant sera). (24,25)

Another issue that remains to be addressed is how best to impute a putative correlate of protection for serotypes that are included in the hexavalent vaccine but have a low incidence of invasive disease (serotypes Ib, II, IV), militating against establishing a serotype-specific correlate of protection for these serotypes in natural epidemiology studies. This could be addressed by estimating a single, putative sero-correlate across all serotypes, in addition to investigating for serotype-specific correlates for those serotypes with high incidence (i.e. serotypes Ia and III). Notably, the putative sero-correlate of protection for PCV, was a composite analyses across all seven serotypes included in the initial PCV formulation (20). Although Andrews et al subsequently estimated serotype-specific correlate of protection, some of which differ in either direction from that proposed initially(26), the initial composite correlate of protection remains the benchmark for evaluation and licensure of new PCV formulations. Furthermore, a single correlate of protection should be established for GBS-EOD and GBS-LOD, especially considering the narrow window period during which these cases occur (i.e. <3 months of age). The validation and refinement of these sero-correlates of protection could be undertaken in phase IV studies that evaluate the effectiveness of GBS vaccine against invasive disease following licensure and introduction of GBS into maternal immunization programs.

The RMPRU has previously undertaken a cross-sectional study to investigate correlates of protection against invasive GBS disease in infants in Soweto(27). In the initial study, we were able to derive estimates of maternal serotype specific capsular antibody associated with reduced risk of invasive GBS disease by serotypes Ia and III in their infants. A limitation of this study included cases only being enrolled following culture-confirmation, rather than blood samples being available at a baseline period (e.g. cord or maternal blood at birth), and the inability of understanding how this could have affected the serotype-specific IgG threshold associated with reduced risk of disease. Also, the limited number of cases, resulted in wide uncertainty bounds around the threshold associated with invasive disease. A further limitation of this (and all other previous studies), was the absence of a standardized assay to measure antibody levels; which is necessary for cross-

comparisons between studies and for a sero-correlate to be universally acceptable – including by regulatory authorities if vaccine-licensure is to be based on safety and immunogenicity. The RMPRU is currently part of a collaboration in establishing such a standardized assay for capsular antibody measurement, which will be available by mid-2019 (Personal communication, Kirsty Le Doare, Lancet ID in press).

In addition to the above study, RMPRU subsequently enrolled a cohort of 35,000 mother-newborn pairs between July 2014 and December 2016 (V98_28OBTP study) to further investigate correlates of protection against invasive GBS disease in the infants (HREC reference 140203, Clinicaltrials.gov reference NCT02099149). The primary objective of the study was to define a correlate of protection against serotype Ia and III GBS-EOD. Although this study provided similar estimates of the threshold associated with protection against invasive GBS disease compared to the earlier cross-sectional study(27), this study also did not achieve the targeted sample size of prospectively enrolled cases. The protocol-defined targeted number of at least 20 cases of invasive GBS disease due to each of serotypes Ia and III, would have provided 80% power to detect 90% reduction in risk of invasive disease by serotype among the infants.

The V98_28OBTP study also enrolled cases retrospectively (i.e. collection of maternal and infant blood samples within 72 hours after having culture confirmed invasive GBS disease diagnosed in the infant), similar to what was done in the earlier cross sectional study. Furthermore, serotype-specific antibody levels in the V98_28OBTP study was evaluated using the RMPRU in-house assay, which is yet to be benchmarked against the soon to be established standardized assay.

Briefly, the number of cases and serotype distribution of enrolled cases and number of matched controls (i.e. women colonized with the serotype, but whose infants were free of disease) in the V98_28OBTP study is summarized below.

Table 1: Number of samples from mothers and infants of cases and controls enrolled in V98_28OBTP study eligible for inclusion in the sero-correlate of protection analysis.

		Cohort group	Retrospective cases	Total

		Case	Control	Case	Control	Case	Control
EOD	Ia	8	32	4	16	12	48
	III	10	36*	7	25	17	61**
	V	4	16	1	4	5	20
	Ib	0	0	1	4	1	4
	II	4	12	3	12	7	24
	IV	1	3	0	0	1	3
LOD	Ia	3	12	3	12	6	24
	III	10	37*	12	43	22	80**
	V	0	0	0	0	0	0
	Ib	0	0	0	0	0	0
	II	0	0	0	0	0	0
	IV	0	0	0	0	0	0
Total	Ia	11	44	7	28	18	72
	III	20	73**	19	68	39	141**
	V	4	16	1	4	5	20
	Ib	0	0	1	4	1	4
	II	4	12	3	12	7	24
	IV	1	3	0	0	1	3

* Three controls were twins. The mom's sample was only used once.
** Numbers affected by twins.
EOD: Early onset disease; <7 days of age.
LOD: Late Onset Disease; 7-89 days of age.
Case: Invasive disease with isolate identified from a normally sterile site.
Control: Mother matched by age-group, gestational age, HIV infection status, and colonization by homotypic serotype due but whose baby was free of invasive disease.
Prospective: Cord blood from cases and all controls obtained at time of birth, and maternal blood collected within 12 hours of birth.
Retrospective: Cases (and their mothers) in whom the blood sample was only collected after the case was confirmed by culture of a usually sterile site in the laboratory.

A total of 35 evaluable invasive GBS cases were identified from the prospectively enrolled cohort, including 18 cases of EOD and 13 LOD cases of serotype Ia and III combined. Together with the retrospectively enrolled cases, there were 29 GBS-EOD (12 Ia and 17 III) and 22 GBS-LOD (III) cases. Provisional analyses of the results from the V98_28OBTP study indicated that the antibody concentration in prospectively and retrospectively obtained samples associated with 90% reduced risk of serotype Ia invasive GBS EOD and LOD disease was 5.9µg/ml in maternal blood sample; but lower in infant blood samples (2.1µg/ml). In contrast, for serotype III, the maternal and infant blood samples associated with 90% reduced risk of the infant having invasive GBS disease were similar (1.9 and 1.7 µg/ml, respectively); albeit both these thresholds being lower than for serotype Ia. In further analyses, we

demonstrated that the inclusion of “retrospective” enrolled cases in these estimates inflated the maternal antibody concentration associated with protection against invasive disease in their infants; but not so for the infants (i.e. the threshold remained similar when limiting analyses only to prospectively enrolled cases [cohort], compared to inclusion of samples from the retrospectively enrolled cases). These findings have implications for design of future studies, including highlighting the need to focus on infant blood samples for establishing a correlate of protection rather than maternal blood. Furthermore, the similar findings when including the retrospectively enrolled cases with the cohort cases, lends itself to enrolling more invasive GBS cases, without the complexity and cost incurred for obtaining cord blood on all births. Also, there was less difference in the antibody concentration predicted of 90% reduced risk for invasive GBS disease for serotypes Ia and III in the infant samples (2.1 vs 1.7 µg/ml) compared to observed for the maternal concentrations (5.9 vs 1.9 µg/ml; respectively).

In an effort to bolster the evidence base of establishing a sero-correlate of protection against invasive GBS disease in infants, and taking into consideration the findings from our previous studies, we now propose enrolling another cohort of 20,000 mother-infant dyads. In parallel, we plan to enroll invasive GBS cases beyond the group of infants enrolled into the birth cohort, to increase the number of invasive GBS disease cases enrolled. The enrolment of these “retrospective cases” will include multiple facilities across South Africa, to optimize the ability of the study to derive a correlate of protection for the composite of GBS-EOD and GBS-LOD; that is primarily based on infant serum antibody measure using the standardized GBS IgG antibody assay.

2. Correlates of Protection Study Objectives

2.1 Primary objective

- Determine the infant GBS serotype Ia and III specific capsular serum IgG antibody level associated with 80% reduced odds of invasive GBS disease between 0-89 days of age for the combined “cohort” and “retrospectively enrolled” cases.

  Endpoint: Estimated odds of disease for infants with GBS serotype specific Ia and III capsular serum IgG antibody levels above a threshold and estimated odds of

disease for infants with GBS serotype specific Ia and III capsular serum IgG antibody levels below the threshold.

2.2. Infant Secondary Objectives:

2.2.1 Determine the infant GBS serotype Ia and III specific capsular serum IgG antibody level associated with 80% reduced odds of invasive GBS disease between 0-89 days of age, stratified for "cohort" and "retrospectively enrolled" cases.

Endpoint: Estimated odds of disease for infants with GBS serotype specific Ia and III capsular serum IgG antibody levels above a threshold and estimated odds of disease for infants with GBS serotype specific Ia and III capsular serum IgG antibody levels below the threshold, stratified for cohort and retrospectively enrolled cases.

2.2.2 Determine the infant GBS serotype Ia and III specific capsular serum IgG antibody levels associated with 80% reduced odds of invasive GBS disease for cohort and retrospectively enrolled cases combined, stratified by GBS-EOD and GBS-LOD.

Endpoint: Estimated odds of disease for infants with GBS serotype specific Ia and III capsular serum IgG antibody levels above a threshold and estimated odds of disease for infants with GBS serotype specific Ia and III capsular serum IgG antibody levels below the threshold stratified by GBS-EOD and GBS-LOD.

2.2.3. Determine the infant GBS capsular serum IgG antibody levels associated with 80% reduced risk of invasive GBS disease for the composite of all serotypes in the cohort and retrospectively enrolled cases combined.

Endpoint: Estimated odds of disease for infants with GBS serotype specific capsular serum IgG antibody levels above a threshold and estimated odds of disease for infants with GBS serotype specific Ia and III capsular serum IgG antibody levels below the threshold. The same threshold will apply to different serotypes.

2.2.4. Determine the infant GBS serotype Ia and III opsonophagocytic activity (OPA) titre associated with 80% reduced odds of invasive GBS disease between 0-89 days of age for the combined “cohort” and retrospectively enrolled cases.

Endpoint: Estimated odds of disease for infants with GBS serotype specific Ia and III OPA titres above a threshold and estimated odds of disease for infants with GBS serotype specific Ia and III OPA titres below the threshold.

2.3. Maternal Secondary Objectives:

2.3.1. Determine the maternal GBS serotype Ia and III capsular serum IgG antibodies associated with 80% reduced odds of invasive GBS disease in their infants between 0-89 days of age.

Endpoint: Estimated odds of disease for infants with maternal GBS serotype specific Ia and III capsular serum IgG antibody levels above a threshold and estimated odds of disease for infants with maternal GBS serotype specific Ia and III capsular serum IgG antibody levels below the threshold.

2.3.2. Determine the maternal GBS serotype Ia and III capsular serum IgG antibodies associated with 80% reduced odds of invasive GBS disease in their infants stratified by GBS-EOD and GBS-LOD.

Endpoint: Estimated odds of disease for infants with maternal GBS serotype specific Ia and III capsular serum IgG antibody levels above a threshold and estimated odds of disease for infants with maternal GBS serotype specific Ia and III capsular serum IgG antibody levels below the threshold, stratified by GBS-EOD and GBS-LOD.

2.3.3. Determine the maternal GBS capsular serum IgG antibody levels associated with 80% reduced odds of invasive GBS disease for the composite of all serotypes.
Endpoint: Estimated odds of disease for infants with maternal GBS serotype specific capsular serum IgG antibody levels above a threshold and estimated odds of disease for infants with maternal GBS serotype specific capsular serum IgG antibody levels below the threshold.

2.3.4. Determine the maternal GBS serotype Ia and III opsonophagocytic activity (OPA) titre associated with 80% reduced odds of invasive GBS disease between 0-89 days of age for the combined “cohort” and retrospectively enrolled cases.

Endpoint: Estimated odds of disease for infants with maternal GBS serotype specific Ia and III OPA titres above a threshold and estimated odds of disease for infants with maternal GBS serotype specific Ia and III OPA titres below the threshold.

Note: For cases, maternal samples could be available from the time of delivery or from the time of diagnosis of the GBS case, depending on the timepoint of enrolment i.e prospective or retrospective enrolment. All maternal endpoints will be analysed using the composite data from prospectively (cohort) and retrospectively enrolled cases; and stratified by timing of enrolment.

2.3.4. Describe the prevalence of recto-vaginal GBS colonization at time of labour, and stratification by maternal HIV status.

2.4 Redacted

2.5. Non-immunological secondary study objectives specific to cohort participants

2.5.1. Describe the incidence of culture confirmed invasive GBS disease up to 89 days of age, in live births among infants up to 89 days of age, born to women enrolled in the cohort study.2.5.2. Describe the incidence of culture confirmed GBS disease in women enrolled in the cohort study.

3. Study Design and Methods:

3.1. Study population:

3.1.1. Population of Cohort study

The cohort of 20,000 mother-newborn dyads will be enrolled at Chris Hani Baragwanath Academic Hospital (CHBAH) and Rahima Moosa Mother and Child Hospital in the City of Johannesburg, South Africa.

The population of Soweto is estimated at 1.2 million, including an annual birth cohort of 28,000. The majority (99%) of deliveries in Soweto occur at public health facilities, where health care is provided at no cost to all pregnant women and children by the State. Three quarters of all births in the public health sector in Soweto occur at CHBAH and the others at one of 5 midwife operated units (MOUs) or the Bheki Mhlangeni District Hospital (BMDH). Furthermore, there is a low threshold for referrals from the MOUs to the hospital if any signs of imminent obstetric complications are observed before or during labour, including women in preterm labour. Also, there is a low threshold for referring ill neonates from the surrounding primary health care clinics to CHBAH for management. Facilities at CHBAH include a neonatal intensive care unit where invasive and non-invasive mechanical ventilator support is available.

The prevalence of HIV among pregnant women in Soweto has remained unchanged at 28-29% over the past decade. Improved HIV prevention strategies has, however, resulted in mother-to-child HIV transmission rates declining from 8% in 2004 to 1.1% by 2015. The neonatal mortality rate in Soweto, based on a longitudinal cohort study from 2011 was estimated to be 22 per 1000 live births (unpublished data from Matflu study), which was higher than the national rate of 14 per 1000 live births estimated for South Africa in 2015.

Rahima Moosa Mother and Child Hospital (RMMCH) is located in Coronationville, in the City of Johannesburg region B. RMMCH offers obstetrics, gynaecology and paediatric care to the population of Western Johannesburg. The COJ region B has a diversity of housing, including historic, upmarket residences, university

accommodation and poverty-stricken areas. The population of region B is ~198,000, however some of the higher income earners residing in the region will access health care from one of the local private hospitals (e.g. Millpark, Garden City clinic). The low and middle income communities in the region usually access public clinics and hospitals for health care. There were 12,863 deliveries at RMMCH in 2017. Of all deliveries in 2017, 60% were normal vaginal deliveries, 1.9% assisted vaginal deliveries, and 38.2% were delivered by caesarian section (RMMCH statistics: 2017).

The demographics of the population serviced by RMMCH is mixed, with patients from black, white, Asian and mixed race groups utilizing the facility. Forty-one percent of mothers delivering at RMMCH in 2017 were not South African. The prevalence of HIV in antenatal attendees in the population served by RMMCH is 19%, which is lower than the overall HIV prevalence in the City of Johannesburg.

3.1.2 Retrospective Case enrolment

In addition to surveillance for invasive GBS disease in infants ≤89 days of age at CHBAH and RMMCH among newborns born to women enrolled in the Cohort group, we will also enrol cases of invasive GBS disease in infants not enrolled in the cohort (i.e. retrospectively identified invasive GBS cases) at these facilities. Also, we will expand surveillance for identification and enrolment of invasive GBS cases to other facilities across South Africa, including Charlotte-Maxeke Johannesburg Academic Hospital (CMJAH, Johannesburg), Hospitals in the Tshwane Academic Laboratory network (Steve Biko, Kalafong, Tembisa, Mamelodi and Pretoria West) (Tshwane),Tygerberg Hospital (Stellenbosch), Mowbray Maternity Hospital in Cape Town and Prince Mshiyeni Memorial Hospital in Durban. Additional sites might be included during the course of the study, if we identify through the National Health Laboratory Service (NHLS), more than 15 infants with invasive GBS cases per annum from any particular hospital. All the centers enrolling cases retrospectively are hospitals in which laboratory services are provided by the NHLS with standardized selective culture methods to identify GBS

3.2. Enrolment into Cohort study

Enrolment into the cohort study will occur at the antenatal clinics based at CHBAH and RMMCH and at community antenatal clinic serving the community that deliver at CHBAH and RMMCH. Pregnant women will be approached for enrolment of themselves and their newborns at the time of attending antenatal clinics, during the early stages either of labour or immediately post-delivery. The University of the Witwatersrand Human Research Ethics committee (HREC) approved this strategy for enrolment for the V98_28OBTP study. Approximately 20 000 mother-newborn dyads will be enrolled at CHBAH (n=10,000-15,000) and RMMCH (n=5,000-7,000) over an 18-24-month period, anticipated to start in the first quarter of 2019.

Women consenting to enroll in this study will be screened for eligibility based on planned delivery center, irrespective of gestational age staging and underlying co-morbidities for which clinical information will be collected at the time of enrolment and/or at the time of delivery.

There will be two opportunities at which to consent and enrol subjects into the study cohort:

1. During attendance for antenatal care: Pregnant women will be approached for enrolment into the study at the antenatal clinics of CHBAH and RMMCH as well as at community clinics in Johannesburg including as Lillian Ngoyi Clinic (LNC), Diepkloof, Mofolo, Michael Maponya, Zola, Itereleng and Chiawelo clinics in region D, and Discoverers and OR Tambo in region B. The majority of women booking at these community-based Johannesburg antenatal clinics from which participants will be enrolled, deliver their babies at CHBAH or RMMCH respectively.

2. At delivery in participating centers: Women may be consented during early stages of labour or immediately post-delivery. If a mother is identified during active phase of labour, written consent will not be obtained during labour, however, mother will be informed about the study, and if she gives verbal consent, cord blood will be collected prior to written consent. Written consent will be obtained from the mother for inclusion into the study, within 24 hours of delivery, or once she is comfortable and able to engage in the informed consent process. Cord blood

samples collected from newborns whose mothers refuse to sign written consent after delivery, will not be tested for study purposes and will be tracked and discarded. This strategy has been previously approved by the local Ethics Review committee (HREC protocol numbers: M120963/M120905/ 140203), in the context that it is not practical to consent women in the midst of labour and the procedures involving the collection of cord blood pose no discomfort, are safe and non-invasive. All maternal blood samples and recto-vaginal swab samples will be collected post consenting.

Participants who are enrolled antenatally and go on to deliver in another center will be withdrawn from the study; however, clinical records of the delivery details will be sought from the delivering hospital.

3.2.1. Inclusion criteria at time of study enrolment or delivery for inclusion into cohort group.

1. Pregnant women attending for antenatal care at one of the participating antenatal-clinics and/or delivering at CHBAH or RMMCH.
1. Subjects aged ≥18 years or alternatively, if mother is <18 years of age, consent signed by participants parent or partner/spouse or other legally acceptable guardian, with assent co-signed by under-age mother.
2. Able to understand and comply with planned study procedures.
3. Provides written informed consent.

3.2.2. Exclusion criteria

1. Refusal to consent to study participation.
2. Receipt of any blood products in the past 4 weeks or anticipated during labour.
3. Participant enrolled in any GBS vaccine trial.

Screening registries will be completed for all women approached for study participation, and include detailing reasons for non-participation, if applicable. Participants meeting inclusion and exclusion criteria will be eligible for enrolment into the mother-newborn cohort, irrespective of gestational age staging and underlying co-morbidities.

3.2.3. Censoring criteria for inclusion as cases or controls among those enrolled into the Cohort study

Certain criteria that could constitute an exclusion criterion may only be assessable later in the study. These are defined as criteria for censoring from the Final Analysis Population and include:

1. Exposure to intrapartum antibiotics at delivery: defined as intravenous penicillin, ampicillin, cefazolin, clindamycin or vancomycin for ≥4 hours before delivery (only for the control group). These represent United States Centers for Disease Control and Prevention (CDC) guidelines for prophylaxis for the prevention of GBS in newborns(28). This criterion will be applied to all mother-infant dyads that are potential controls, but not to invasive GBS cases (or their mothers). This is to militate against selection of controls in whom the risk of disease in the infant was prevented through antibiotics given to the mother.
2. Blood transfusion or receipt of any other blood products in the 30 days before delivery in the mother.
3. Maternal participants whose foetus or infant is diagnosed with a severe congenital malformation considered by the attending physician to be inevitably fatal during perinatal period.

3.3. Sample collection for cohort participants

Participants enrolled in the cohort will have samples collected during the delivery admission as follows:

- Maternal blood sample
- Maternal vaginal and rectal swab
- Cord blood
- Nasopharyngeal swab (self-administered)

Participants enrolled in the cohort and who are found to be colonized with GBS on the recto-vaginal swab will have samples collected 7 -14 days post-delivery as follows:

Logs of all infants <90 days of age identified as GBS cases will be maintained. Reasons for non-enrolment will be recorded.

3.4. Sample collection for invasive GBS or (Cohort and for retrospectively enrolled cases):

All GBS isolates of enrolled participants will be retrieved from the local NHLS laboratories for archiving and further serotype characterization using a latex agglutination test for GBS (see section 6.).

3.5. Surveillance of Cohort participants for suspected serious bacterial infections, including hospital-acquired infections.

Infants born to women enrolled in the Cohort study will be followed-up to ≤89 days of age for all cause hospitalization and death. This will involve hospital-based surveillance for hospitalization, and an end-of-study phone call to confirm the well-being of the child during the first three months of life. The hospital based surveillance will involve:

- Daily review and screening of all admissions of infants ≤89 days to the neonatal and paediatric wards at CHBAH and RMMCH.
- Cross matching of admitted infants and their mothers with GBS-CoP cohort using numerous methods including probability matching of names, surnames and hospital numbers.
- Abstraction of medical history, details of examination, sign and symptoms, laboratory results, progress and treatment from medical notes and laboratory results throughout the admission.
- Completion of case report form documenting each episode of sepsis during the admissions, including data on signs, symptoms and laboratory results.

3.6. Surveillance of Cohort participants for invasive GBS disease in maternal participants

All GBS isolates of enrolled maternal participants in the first 90 days post-partum will be retrieved from the local NHLS laboratories for archiving and further serotype

characterization using a latex agglutination test at the RMPRU laboratory (see section 6).

4. Sample size calculation

The sample size was calculated to detect an 80% reduction in the risk of EOD or LOD by serotype Ia or III among infants, with 80% power, based on the ratio of cases to controls with maternal antibody levels above a specified titer versus the ratio of cases to controls with antibody levels below the specified protective titer. Calculations were based on method described by Walter for matched case control studies(29).

The overall prevalence of vaginal colonization between 2004-2008 at delivery in Soweto in a cohort of 5099 mothers was 20.7% (n=1 055) in 2005-2007(30). More recent results from Soweto indicate a similar prevalence of vaginal colonization at delivery, and reported on persistence, loss of and new acquisition of GBS rectovaginal colonization during the second half of pregnancy(31). The proportional contribution of each serotype to newborn and maternal colonization at CHBAH has been described(32). Based on these data we anticipate needing to swab at least 1200 women in the colonization studies, which will provide us with 80 and 100 newborns of mothers colonized with serotypes Ia and IIII, respectively, who did not developed GBS disease (controls). The serotype distribution and other matching criteria with the mothers who are vaginally swabbed will be reviewed periodically to ensure that the target of enrolling at least 4 controls with the same serotype to each case of serotype 1a and III invasive disease is achieved.

The final sample size is given in Table 2 assumes a study of independent cases and controls with 4 controls per case. Assuming the probability of exposure (e.g. percentage of subjects with antibody level above a specified threshold) among controls is 0.20 and the true odds ratio for probability of exposure in cases versus controls is 0.1, we will need 34 case subjects per serotype; and 180 control subjects to reject the null hypothesis that this odds ratio equals 1 with probability (power) 0.8. The Type I error probability associated with the one-sided test of this

null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate the null hypothesis. These represent the most conservative assumptions.

Table 2: Required number of cases (based upon 4 controls per case) to detect 80, 85 and 90% reductions in risk of disease, assuming 80% power, under different assumptions of the frequency of exposure (proportion of controls with antibody above threshold)

Percent risk reduction	Frequency of exposure among controls (%)	Required Number of Cases	No. of controls per case
80	10	64	4
80	15	44	4
80	20	34	4
85	10	56	4
85	15	38	4
85	20	29	4
90	10	49	4
90	15	33	4
90	20	26	4

Our study is sufficiently powered under the assumptions outlined in this section. If the percentage of controls with antibody levels above the protective titer falls below 20%, the number of cases will not be sufficient to obtain 80% power and enrolment will need to be extended.

As the protective threshold has yet to be determined in this population, the number of cases accrued will be reviewed periodically during the course of the study, as well as the latest independent data external to the study generated on serotype-specific GBS capsular antibody distributions. These data will be used to assess the level of risk reductions the study will be adequately powered to detect and whether enrolment needs to be continued past the anticipated 18-month period.

5. Study definitions

5.1. Study populations

5.1.1. Cohort population

Maternal-newborn dyads enrolled at CHBAH or RMMCH prior to or during delivery-admission, from whom maternal and cord blood are collected.

5.1.2. Control population

Controls will be defined as newborns born to mothers enrolled into the cohort study, whose mother is colonized by a serotype homologous to that of a case to which they matched, but who do not develop invasive GBS disease within 90 days of life. Cases and controls will matched by serotype, gestational age (34-<37 weeks and ≥37 weeks gestation) and maternal age (<25 years, 25-<35 years and ≥35 years). Maternal HIV infection status will be assessed as an effect modifier.

5.1.3. Prospective GBS cases

Infants enrolled in cohort population who develop GBS-disease between birth and ≤89 days of age.

5.1.4 Retrospective GBS case

Infants who are admitted to one of the participating hospitals with GBS-disease diagnosed between birth and ≤89 days of age, and are enrolled onto the study only after identification of GBS-disease.

5.1.5. Early onset GBS disease case

Culture-confirmed GBS-disease with identification of GBS from normally sterile site in a neonate aged 0 to ≤6 days of age.

5.1.6. Late onset GBS disease case

Culture-confirmed GBS-disease with identification of GBS from normally sterile site in a neonate aged 7 to ≤89 days of age.

Cases of invasive GBS EOD and LOD not enrolled prior to the onset of disease, will be eligible for enrolment as retrospective cases. This will be dependent on the invasive isolate being retrievable and the availability of the mother for consenting and providing a maternal blood and vaginal swab sample within 24 hours of GBS case confirmation. A blood sample will also be sought from the infant. The

consenting of these mothers and their infants will involve a separate informed consent procedures compared to the rest of the cohort. However, as prospectively collected maternal and cord blood from the time of delivery will not be available, these cases will only be included in secondary analyses.

5.2. Assessment of gestational age at delivery

The GAIA definition for gestational age assessment (33) will be utilized for this study

Definitions of terms used:

- Ultrasound (U/S):
  - 1st trimester (≤13 6/7 weeks).
  - 2nd trimester scan (14 0/7–27 6/7 weeks).
  - 3rd trimester (28 0/7 + weeks).
- LMP (last menstrual period) –
  - Gestational age is calculated from the first day of the mother's last menstrual period.
  - If LMP and U/S do not correlate, default to U/S GA assessment
  - Certain LMP: (LMP date + 280 days): Use LMP if within 7 days at ≤14 weeks; within 14 days at ≤26 weeks; within 21 days beyond26 weeks.
  - Uncertain LMP – first trimester (≤13 6/7 weeks by LMP): Use the approximate date of the last menstrual period (LMP) if corroborated by physical exam, or a first trimester ultrasound.
    - If there is a discrepancy of >7 days between the LMP and the first trimester ultrasound, the ultrasound-established dates will take preference over LMP for gestational age dating.
  - Uncertain LMP – second trimester (14 0/7–27 6/7 weeks by LMP): Use the approximate date of the LMP if corroborated by physical exam including fundal height, or a second trimester ultra-sound.
    - If there is a discrepancy of >10 days between the LMP and the second trimester ultrasound, the ultrasound-established dates will take preference over LMP for gestational age dating.
  - Uncertain LMP – third trimester >28 weeks – third trimester ultrasound.

- No LMP date: If menstrual dates are unknown, the ultrasound-established dates will be used for gestational age dating or 2nd trimester fundal height and/or newborn physical examination.

Assessment of gestational age(33)

Level 1: (highest level of certainty)

1. Certain LMP* or intrauterine insemination (IUI) date or embryo transfer (ET) date with confirmatory 1st trimester scan (≤13 6/7 weeks). OR
2. 1st trimester scan (≤13 6/7 weeks).

Level 2A

1. Certain LMP* with 2nd trimester scan (14 0/7 weeks to 27 6/7weeks).

If LMP and U/S do not correlate, default to U/S GA assessment. OR

2. Certain LMP* with 1st trimester physical examination.

Level 2B

Uncertain LMP with 2nd trimester scan (14 0/7 weeks to 276/7 weeks).

Level 3A

1. Certain LMP with 3rd trimester scan – 28 0/7 weeks +. OR
2. Certain LMP with confirmatory 2nd trimester FH. OR
3. Certain LMP with birth weight. OR
4. Uncertain LMP with 1st trimester physical examination.

Level 3B

1. Uncertain LMP with FH. OR
2. Uncertain LMP with newborn physical assessment. OR
3. Uncertain LMP with Birth weight

Table 2 Redacted

Table 3: Redacted

5.3. Telephonic follow up

The parents of newborns born to GBS colonized mothers will be contacted by telephone or home visit by study personnel one and three months (28-35 days and 80-100 days) after delivery to ascertain the health status of each infant. In addition,

clinical and microbiological records of participating hospital(s) will be inspected. The purpose is to determine if the infant has suffered any illness compatible with GBS since discharge from the hospital, including hospitalization for any suspected bacterial infection. Controls confirmed for invasive GBS disease or hospitalization for any suspected bacterial infection will be excluded from the colonized control group; although they may be eligible to be potential cases. The 90-day follow-up will also be used to confirm the health status of identified cases.

6. Sample collection and Laboratory Methods

6.1 Blood specimens

Maternal Blood Collection:

Maternal blood (10-15ml) will be collected in SST tubes via venipuncture during delivery admission. Maternal blood should be collected prior to delivery when possible, otherwise blood will be collected post-delivery, ideally within 6 hours after delivery and not more than 24 hours post-delivery. This blood shall be designated for this research project (primary specimen) and shall be collected in addition to any other routine blood that is collected for the women admitted for labour and delivery. Sera will be separated (see 6.2) and stored until confirmation of case control status at RMPRU. The responsibility for processing and storage of the sera prior to case control identification lies with the RMPRU laboratory. Serum from all eligible cases and controls will subsequently be retrieved.

Cord Blood Collection:

Cord blood (10-15ml) shall be collected in SST tubes from an umbilical vessel after double clamping of the cord for this research project. In addition, any residual routine blood that is collected on all infants within 24 hours of birth shall serve as a back-up sample for each infant if the cord-blood collection had not been done or was unsuccessful. Sera shall be separated (see 6.2) and stored until confirmation of case control status at RMPRU. The responsibility for processing and storage of the sera prior to case control identification lies with the RMPRU laboratory.

6.2. Separation of sera from maternal and cord blood

Maternal and cord blood, collected in SST tubes, will be kept refrigerated prior to transport to the laboratory for processing. The specimen will be processed within 4-6 hours of blood drawing. If processing of the blood cannot be done within this timeframe, the blood can be kept in the refrigerator for up to 24 hours and can then be spun down. Sera will be decanted and stored at -18°C or lower. This procedure should eliminate the problem of haemolysis of maternal and cord blood, which may occur with delayed separation of sera.

Reserve Specimen:
In the event of cord-blood not being available for cases with invasive GBS disease, any residual sera from routine standard-of-care tests at the local laboratories will be retrieved and stored at RMPRU. These sera should have been obtained within 24 hours of the time when the culture was undertaken. These samples shall be processed, though they will not form part of the primary analysis dataset.

6.3 Retrieval and storage of case and control sera prior to shipping

Once an infant becomes identified as a potential case (isolation of GBS from a normally sterile site) or a potential control, the sera shall be retrieved and tested at RMPRU for serotype specific IgG (Ia, Ib, II, III and V) with the standardized multiplex Luminex platform. At least one aliquot of sera (volume allowing) from infants and their mothers who did not become potential cases or colonized controls will be retained at the RMPRU laboratory in South Africa and will be archived for up to 25 years. Further testing of these samples for studies focusing on determinants of maternal, foetal, newborn and young-infant health will be undertaken subject to approval of any such protocols by the Ethics Review Board. The responsibility for long term storage of these (non-case, non-control) sera lies with the Principal Investigator and these samples will be stored at the RMPRU, South Africa.

6.4. GBS isolation from blood and CSF cultures (cases)

GBS isolates from a normally sterile site obtained from neonates will be obtained from the microbiology laboratory at each participating hospital. The microbiology laboratory will be monitored on a daily basis for sterile site cultures containing these

organisms. Blood and CSF GBS isolates, as well as GBS isolates from another normally sterile site, will be identified through standard-of-care procedures undertaken by the attending physicians and identified by routine accredited methods. GBS cultured from a sterile site (blood or CSF or other) is undertaken by the National Health Laboratory Service, which is the sole service provider laboratory to the participating hospitals and is certified by the South African National Accreditation Society (SANAS). At participating study centre hospitals, blood is inoculated into a Bactec bottle at the infant's bedside and processed through a Bact/Alert microbial system (Organon Teknika, Durham, NC). A positive specimen is then plated on blood and chocolate agar and observed for colony growth for a period of 72 hours. CSF specimens obtained from the infant are Gram stained and then directly plated onto blood, chocolate agar plates and inoculated into an enrichment broth and observed for colony growth for 72 hours. In addition, direct susceptibility is done as per laboratory standard operating procedure, according to Clinical and Laboratory Standards Institute (CLSI) guidelines (Wikler, 2007). A sample of each GBS isolate will be saved for serotyping and molecular characterization of the isolates.

6.5 Maternal recto-vaginal swab collection

Rectal and vaginal swabs will be obtained on admission for delivery from a subset of mothers enrolled in the study at each participating center. This will occur during pre-determined weekly sampling periods. Mothers will be guided on how to self-collect swabs.
(Appendix 1: Instructions for the collection of a genital swab for the detection of a group B streptococcus (GBS), accessed 30th Oct 2018 (https://www.cdc.gov/groupbstrep/downloads/gbs_swab_sheet21.pdf)
And Appendix 2: 'Box 1. Procedures for collecting clinical specimens for the culture of group B Streptococcus (GBS) at 35-37 weeks' gestation'(28)). Alternately, study staff will collect the recto-vaginal swabs.

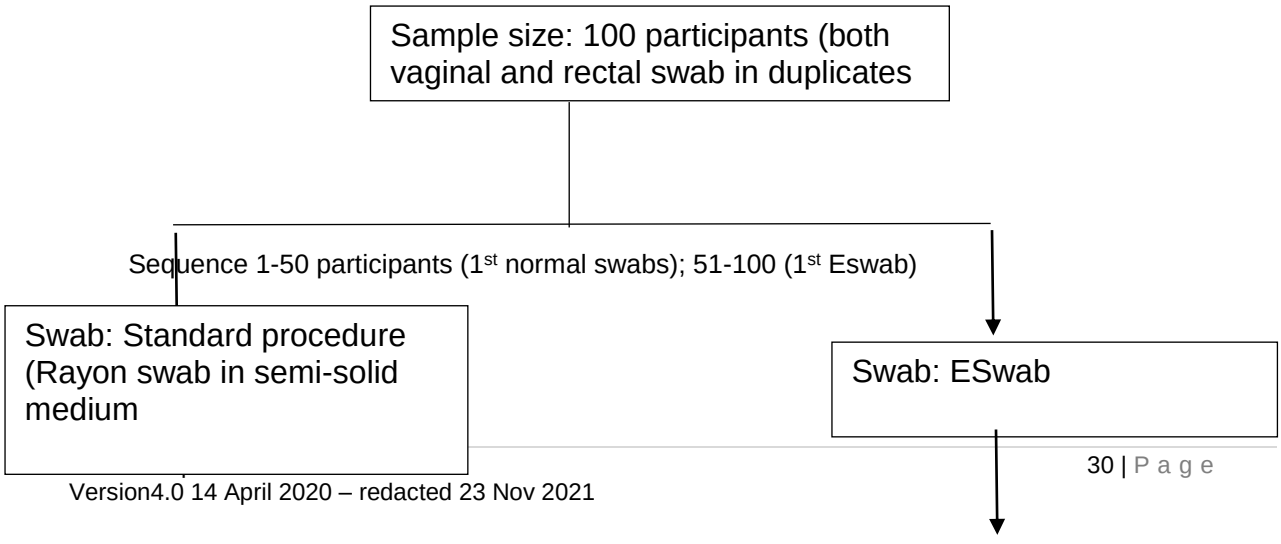
Prospectively enrolled subjects (i.e. with blood taken at delivery) colonized with a GBS serotype and born at ≥34 weeks' gestational age will be eligible to be controls for those cases enrolled with the homologous serotype in the past three-months.

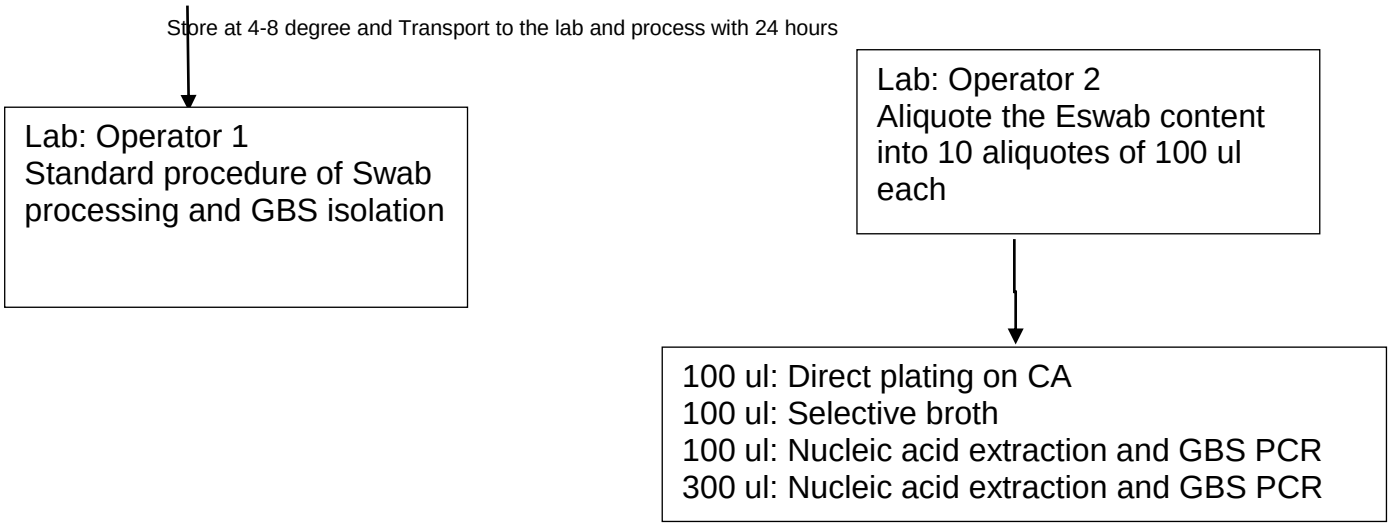
Approximately 4 colonized controls matched by serotype (serotype Ia and III EOD case and serotype III LOD for primary analysis), gestational age and maternal age will be matched to each case during analysis. The addition of matching criteria other than serotype has necessitated an increase in the sample size required in the colonization cohort. As many women as possible still to be enrolled on the study will be swabbed systematically and included in the colonization subset. The number of women to be swabbed will be revised periodically based on ongoing accrual of cases and on the colonization prevalence and serotype distribution of mothers at each study site.

For GBS colonization, duplicate vaginal and rectal swabs will be collected for initial 100 participants using Rayon tipped swab and placed into Amies transport medium without charcoal (Medical Wire Equipment Co. Ltd. Cat: MW170) and nylon flocked tipped swabs using liquid Amies elution swab (Eswab; Copan). The swabs will be transported to the laboratory in cooler boxes by RMPRU drivers and can be refrigerated and stored for a maximum of 48 hours before processing. Swabs will be processed at RMPRU for GBS isolation as per method described in 6.6

Sensitivities for different swabs (detection rates) will be calculated by comparing the proportion of positive samples for each swab in relation to a gold standard, which will be a composite positive for both swabs. Based on the results of this comparison, the swabs with higher sensitivity for GBS colonization will be used for further collection of swabs. The study design for swab comparison is presented in below figure

Study design: Comparison of swabs





6.6 GBS isolation from rectal and vaginal swabs

Swabs will be processed to isolate GBS according to selective culture methodology as recommended by the CDC(28). This will include direct plating on selective media (Chromagar) Plates will be incubated for 18-24 hours at 37°C and then examined for growth of GBS like colony morphologies. If no GBS like colonies are observed, the plates will be further incubated for an additional 24 hours. GBS like colonies will be picked and subjected to further confirmatory tests, such as catalase, growth on bile esculin agar, CAMP (Christie Atkinson Munch-Petersen) test or B antigen latex agglutination testing. Confirmed GBS isolates will be stored in STGG medium at -70°C. GBS isolation from vaginal and rectal swabs will occur at RMPRU laboratory, South Africa.

Rectal and vaginal swab testing will be expanded to include other bacteria, including Recto-vaginal swabs will also be obtained from all women whose newborns are admitted immediately post-birth, if the mother had not already been sampled during labour.

6.7. Storage of pure GBS and procedure for serotyping

GBS isolates from each case and control, as well as maternal recto-vaginal swabs, will be serotyped at RMPRU laboratory, South Africa using a commercial serotyping kit. The test will be based on the principles of co-agglutination: Particles of latex are coated with rabbit antisera specific for GBS serotypes Ia, Ib and II to IX. Two to

three colonies of GBS are picked off an blood agar plate and suspended in 10µl of sterile saline on reaction cards. Equal amounts of antiserum are added and mixed with the bacterial culture. A positive reaction is recorded as any sign of agglutination for that particular serotype. GBS isolates that will test negative by latex agglutination for all serotypes tested will be further molecular typed by PCR using serotype-specific primer sequences as described in table below.

T*able 4: Specific primer sequences for the detection of group B streptococcus capsular types Ia-IX*

Serotype	Sequence (5'-3')	Amplicon size(bp)
Ia	Forward 5'- GGTCAGACTGGATTAATGGTATGC -3' Reverse 5'-GTAGAAATAGCCTATATACGTTGAATGC -3'	1826
Ib	Forward 5'- TAAACGAGAATGGAATATCACAAACC -3' Reverse 5' GAATTAACTTCAATCCCTAAACAATATCG -3'	770
II	Forward 5'- GCTTCAGTAAGTATTGTAAGACGATAG -3' Reverse 5' TTCTCTAGGAAATCAAATAATTCTATAGGG -3'	397
III	Forward 5'- TCCGTACTACAACAGACTCATCC -3' Reverse 5'-AGTAACCGTCCATACATTCTATAAGC -3'	1826
IV	Forward 5'- GGTGGTAATCCTAAGAGTGAACTGT -3' Reverse 5'-CCTCCCCAATTTCGTCCATAATGGT -3'	578
V	Forward 5' GAGGCCAATCAGTTGCACGTAA -3' Reverse 5' AACCTTCTCCTTCACACTAATCCT -3'	701
VI	Forward 5'- GGACTTGAGATGGCAGAAGGTGAA Reverse 5'- CTGTCGGACTATCCTGATGAATCTC	487
VII	Forward 5'- CCTGGAGAGAACAATGTCCAGAT Reverse 5'GCTGGTCGTGATTTCTACACA	371
VIII	Forward 5'- AGGTCAACCACTATATAGCGA Reverse 5'-TCTTCAAATTCCGCTGACTT	282

6.8. Redacted

6.9 Redacted

6.10 Ordering of sera for testing

Maternal and cord sera will first be segregated into paired dyads. For each assay run, sera for cases and controls will be ordered according to a blocked, randomized scheme. This will ensure that testing of cases and controls is temporally balanced.

6.11. Blinding of tests

To blind technicians to the case-control status of tested sera, sera will be labelled with codes that do not indicate the status of the specimen as having been collected from a case or a control.

6.12. Safety procedures

Clinical and laboratory personnel will be trained in the safe handling of bacterial isolates and use of "universal precautions" in the handling of blood and blood product.

7. Data Entry, Management and Analysis

7.1 Data processing and management

All data collected from subjects and provided to the sponsor for analysis must be stripped of any identifiers that reveal the identity of that individual (beyond the use of subject ID).

Screening logs will be maintained at the site. This information is not part of the clinical database management system. Standard Operating Procedures related to screening, enrolment process and Subject IDs management will be developed.

Data will be collected on study-specific data collection forms, and entered into specially designed databases. Internal monitoring and quality assurance will be conducted on important variables and the ICF forms. Edit checks will be performed on the database. This may include logic checks and acceptable ranges around specific variables.

All study data will be entered by the investigator, or delegate (including a contract research organization), who will sign and date the CRFs. If the investigator delegates and authorizes other persons in his/her staff to make entries on the CRF,

the names, positions, signatures and initials must be documented in writing (e.g., site delegation log). CRFs will be completed for each enrolled subject and in a timely manner. Laboratory results will be entered onto CRF's as they become available.

7.1.2 Software and hardware

The following software will be used for the purpose of this study:
SQL, REDCAP STATA (version 12.0), R (version 2.13) or SAS (version 9.4).

7.2 Data analysis

Primary and secondary analyses will consider the combined "cohort" and "retrospectively enrolled" cases and controls born at ≥34 weeks' gestation. The latter aims to ensure the inclusion of infants for whom there has been an opportunity for significant transplacental transfer of maternal IgG antibodies. A linear relationship between log IgG and gestational age has long been established (Evans, 1971). It was demonstrated that GBS type Ia and III IgG antibodies in newborns 34 weeks' gestation or older was significantly higher than in newborns under 34 weeks' gestation. Newborns of any gestational age will be considered in a sensitivity analysis of cord blood antibody levels.

7.2.1 Study cohorts

The study population will be described in terms of the following datasets.

Enrolled Cohort (EC): All subjects who provide informed consent and meet inclusion/exclusion criteria, including both prospectively enrolled ('cohort') and retrospectively enrolled ('cases') participants.

Analysis Cohort (AC): All subjects in the EC, meeting additional eligibility criteria (censorship criteria) assessed during the study, with a prospectively collected maternal or cord blood sample (for 'cohort') or those with maternal and infant blood

sample collected within 72 hours of GBS diagnosis ('for cases') and with gestational age at delivery of ≥34 weeks

Analysis Case Control Set (ACCS): All subjects in the AC meeting case control criteria, with a valid serology result. Retrospectively enrolled cases will be included as the intention is to estimate what the cord blood titre would have been by comparing the serotype specific IgG levels with those cohort participants which have blood samples from 2 time-points, namely birth and at the time of diagnosis of invasive GBS.

7.2.2 Statistical hypotheses

The null hypothesis is there is no difference between odds of disease for those above a specific threshold and those below a specific threshold. The alternative hypothesis is that the odds of disease for infants with antibody concentrations above a specific threshold is less than that for those with antibody concentrations below a specific threshold.

7.2.3 Statistical Methods

<u>Descriptive analysis of study population</u>

Demographic and clinical characteristics will be presented for both cases and controls and for the overall Analysis Cohort (AC) using descriptive statistics (mean, standard deviation, median, minimum and maximum). Students t-tests will be used to compare continuous variables (e.g. maternal age, gestational age etc.) among cases and controls. The chi-square test or Fisher's exact test will be used for to compare the distribution of categorical variables among cases and controls.

The Enrolled Cohort (EC) will be described by enrolment site and whether enrolment is pre-delivery or at delivery. The Analysis Cohort (AC) will be described by enrolment site, timing of disease (EOD or LOD) and by delivery site. The final

Analysis Case Control Set (ACCS) will also be stratified by maternal/newborn sera, age at disease onset (EOD v. LOD) and serotype (Ia or III).

Primary objective:

Only the Analysis Case Control Set (ACCS) will be included in the primary analysis. The case control analysis will be stratified by serotype (Ia or III).

Secondary objectives:

Only the Analysis Case Control Set (ACCS) will be included in the secondary analyses of the outcomes. Case control analyses will be stratified by maternal/cord sera, age at disease onset (EOD or LOD) and serotype (Ia or III) according to the specific objective.

Descriptive analyses*:*

Serotype-specific capsular IgG antibody levels in cases and controls (by maternal/cord blood, age at onset and serotype) will be compared using geometric means (GM) and corresponding 95% confidence intervals.

Graphical representation of the data will be displayed using overlapping histograms and reverse cumulative plots of serotype-specific capsular IgG antibodies for cases and controls.

A trend analysis for antibody levels and for the risk of developing EOD and LOD (by maternal/cord blood and serotype) will be performed using the χ^2 test for trend, with a score equal to the midpoint of the antibody level interval (log scale). The 5% level will be considered statistically significant.

Analytical methods

The association between disease risk and serotype-specific capsular IgG antibodies will be explored using the following measurements:

Adjusted risk reduction

Multiple logistic regression will be used to estimate the reduction in risk of disease associated with a range of pre-determined thresholds (e.g. ≥0.5, ≥1, ≥2, ≥3, ≥4 and ≥5 µg/mL) compared to a reference group (those with antibody concentrations <0.5 µg/mL).

The dependent variable will be the case/control status with maternal antibody titers, as well as potential confounders, as independent variables.

Potential confounders include the stratification factors described above and maternal HIV status. Any other potential confounders will also be sought. Because of the rarity of disease caused by GBS, the relative risk will be estimated by the odds ratio and the risk reduction calculated as:

Risk Reduction: (1-odds ratio) x 100%.

The smallest threshold ensuring a RR of 60%, 70%, 80% and 90% (equivalent to ORs of 0.4, 0.3, 0.2 and 0.1 respectively) will be reported as candidates defining potential correlates of protection against GBS disease. The whole estimated RR curve will be plotted. The final proposed threshold will be associated to the higher statistically significant risk reduction.

Absolute disease risk

Absolute Disease Risk (ADR) estimates will also be generated. The ADR is the estimated probability of serotype-specific EOD or LOD infection for any maternal or newborn/cord antibody concentration threshold. An ADR curve will be generated to describe the predicted serotype-specific EOD/LOD neonatal infection probability over the range of measured maternal antibody concentration thresholds.

The ADR will be calculated using a parametric Bayesian model as described by Carey et al. Nonparametric ADR will be calculated as done by Fabbrini et al(40). which uses Kaplan-meier estimates for antibody distribution of cases and controls as well as the point estimate for disease incidence. Nonparametric bootstrap methods will be used to construct 95% confidence intervals(41)

<u>Methods to control for confounding</u>

Stratification and covariate adjustment within the logistic regression model will be conducted to adjust for confounding. Potential confounders will be identified by the following criteria: if the crude estimate is changed by more than 10% in the univariate analysis with inclusion of the confounder, the confounder will be included in the adjusted analysis.

Methods to control for effect modifications

Due to the small number of expected cases, variables which may modify the effect of maternal antibody titer on case/control status will not be systematically investigated. The exception will be HIV status and maternal infection status. Although there are insufficient published data to understand whether maternal HIV status may affect trans-placental transfer of GBS anti-capsular antibodies), a reduction in the trans-placental transfer of antibodies specific to other infections has been observed within HIV positive women. Maternal GBS colonization has been occasionally been associated with the observation of very high maternal antibody levels at delivery in infants who develop GBS disease(24,42). This is contrary to previous observations of the inverse relationship of capsular GBS maternal antibody levels and risk of infant GBS disease. As such, clinical markers of maternal infection will be explored.

7.2.4 Sensitivity analyses

Other methods available for evaluating case/control data with a small number of cases, including negative binomial regression, will be explored. If alternative statistical methods are explored, a simulation analysis will be performed to compare the alternative methods to those described above. The purpose of the sensitivity analysis will be to assess the robustness of each model, when varying the distribution of maternal titers and the number of cases and controls.

7.2.5 Subgroup analyses

Subgroup analyses will only be considered if the required number of cases can be achieved.

7.2.6 Redacted

7.2.8 Interim analysis

No interim analysis is planned.

7.2.9 Statistical considerations

Some selection bias may be introduced into the study if those mothers refusing consent differ systematically in terms of capsular antibody profile and GBS risk compared to those who do consent for enrolment. However, the impact of this potential bias will be difficult to assess.

The implementation of active surveillance in multiple medical departments and multiple referral hospitals in South Africa should maximize case capture and therefore ensure cases are representative of GBS cases occurring in the population. The active surveillance should also minimize the chance of misclassification of cases and controls. The population-based sampling of controls also aims to maximize the representativeness of controls to the general non-GBS disease population.

In the event of missing case/control status or maternal antibody titer, the patient will be excluded from analyses. The study aims to minimize missing demographic and clinical data through the use of maternal interviews and medical record review.

8. Protection of Human Research Participants

RMPRU respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with applicable laws and regulations.

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by regulatory authorities or their designates.

The results of the samples collected for research purposes (maternal vaginal swabs, maternal and cord blood) will not impact medical management of the maternal or infant subjects, and therefore these results will not be shared with the individual subjects or their health care providers in real-time. Maternal subjects colonized with GBS will, however, be notified about their status as this can impact future pregnancies.

8.1 Anticipated benefits

Participants will not experience direct benefits from this study.

8.2 Confidentiality

Participants in the study will be identified for study purposes with a unique numerical identifier.

8.3 Costs to participants

Participants will incur no extra costs based on participation in the study.

8.4 Review board approval

The protocol and the proposed informed consent form will be reviewed and approved prior to study initiation by the Human Research Ethics Committee, University of the Witwatersrand; and subsequently for any amendments made to the initial protocol or ICF . Relevant approvals from hospital management and relevant provincial departments of health will be obtained prior to study initiation.

8.5. Notification of participants of their individual results

Women who are GBS-colonised at the delivery admission will be informed of their colonization status, specifically to encourage mothers to be vigilant about reporting any signs of sepsis in their newborn to health care worker, and for future pregnancies.

8.6 Intellectual property

Data collected are the property of the University of the Witwatersrand's RMPRU. The data from this study might be used for meta-analysis involving testing of samples from other studies that will be undertaken in USA and UK (and if any others), for a pooled analysis to establish a common correlate of protection across all the studies.

8.7 Disseminating results to the public

Registration in Public Database(s): This study will be registered in the South African National Clinical Trials register (http://www.sanctr.gov.za) as required by South Africa law and at ClinicalTrial.gov .

9 Redacted

Table 5: Redacted

10 Redacted

11 Funding for the study

This study will be co-funded by the Bill and Melinda Gates Foundation (Grant number OPP1197148) and Pfizer.

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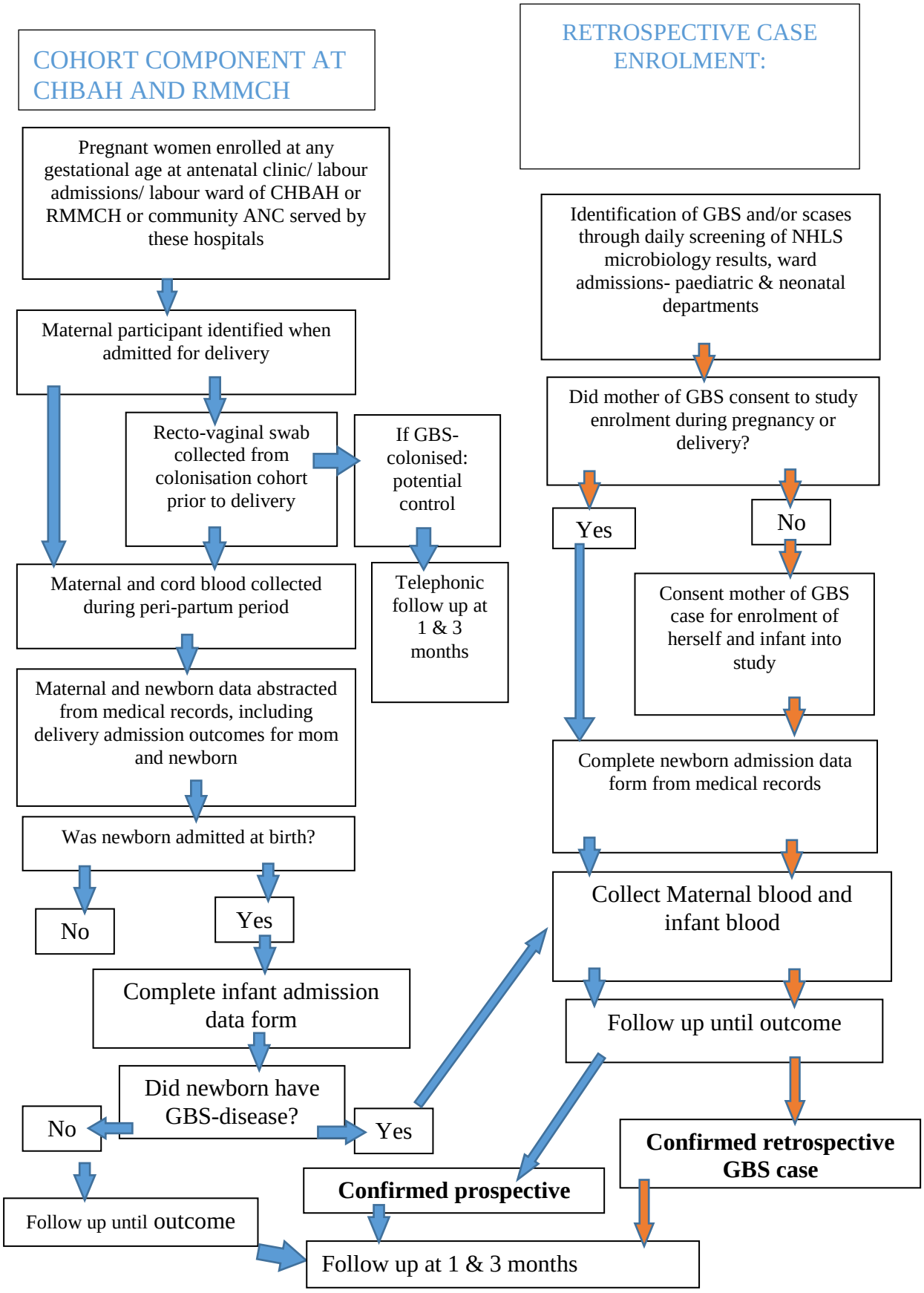
COHORT COMPONENT AT CHBAH AND RMMCH
Pregnant women enrolled at any gestational age at antenatal clinic/ labour admissions/ labour ward of CHBAH or RMMCH or community ANC served by these hospitals
Maternal participant identified when admitted for delivery
Recto-vaginal swab collected from colonisation cohort prior to delivery
If GBS-colonised: potential control
Telephonic follow up at 1 & 3 months
Maternal and cord blood collected during peri-partum period
Maternal and newborn data abstracted from medical records, including delivery admission outcomes for mom and newborn
Was newborn admitted at birth?
No
Yes
Complete infant admission data form
Did newborn have GBS-disease?
No
Yes
Follow up until outcome
RETROSPECTIVE CASE ENROLMENT:
Identification of GBS and/or scases through daily screening of NHLS microbiology results, ward admissions- paediatric & neonatal departments
Did mother of GBS consent to study enrolment during pregnancy or delivery?
Yes
No
Consent mother of GBS case for enrolment of herself and infant into study
Complete newborn admission data form from medical records
Collect Maternal blood and infant blood
Follow up until outcome
Confirmed retrospective GBS case
Confirmed prospective
Follow up at 1 & 3 months

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

Investigational Product Number:	PF-06760805
Investigational Product Name:	Group B Streptococcus 6-Valent Polysaccharide Conjugate Vaccine (GBS6)
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C1091002
Phase:	1/2

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	11 May 2018	Not applicable (N/A)

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APPENDICES

PROTOCOL SUMMARY

Background and Rationale

Streptococcus agalactiae, also known as group B streptococcus (GBS), is an encapsulated, gram-positive coccus that is associated with lower intestinal and rectovaginal colonization. There are 10 serotypes of GBS (Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX) differentiated by the polysaccharide composition of their capsules. Although all GBS serotypes have been found to cause disease, 6 serotypes (Ia, Ib, II, III, IV, and V) have been found to cause over 85% of disease globally and 98% in South Africa, but there is variability in their global prevalence and virulence. GBS disease is most frequently found in the very young—newborns and infants younger than 3 months of age—and the elderly, especially older adults with comorbid conditions. However, disease due to GBS has been reported in individuals of all ages, and pregnant women may be particularly susceptible to GBS disease as well.

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

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

Vaccination of pregnant women has been used globally in the prevention of neonatal tetanus and more recently for prevention of pertussis in young infants, and to protect women and their infants against influenza. Vaccination with tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women was introduced in the United States and in the United Kingdom in response to a significant upsurge in pertussis cases in all age groups. Maternal immunization against influenza was recommended by the US Advisory

Committee on Immunization Practices (ACIP) because of the increased risks of influenza and related complications in pregnant women. Safety surveillance conducted through 2012 has demonstrated no unusual patterns of pregnancy complications or fetal outcomes.

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

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

Primary Objectives

Primary Objective: Stage 1

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

Primary Objectives: Stage 2

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

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

Primary Objectives: Stage 3

- To describe the safety and tolerability of 1 selected dose/formulation of GBS6 when administered to healthy pregnant women 18 to 40 years of age vaccinated at 27 to 36 weeks' gestation.

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

Primary Endpoints

Primary Endpoints: Stage 1

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

- Proportions of nonpregnant women 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 nonpregnant women reporting adverse events (AEs) through 1 month following administration of investigational product.

- Proportions of nonpregnant women reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) through 6 months following administration of investigational product.

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

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

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

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

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

Primary Safety Endpoints (Infants): Stages 2 and 3

- Proportions of infants with specific birth outcomes.

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

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

Study Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of a multivalent GBS vaccine in healthy nonpregnant women and pregnant women aged 18 to 40 years and their infants. A total of approximately 586 subjects (66 nonpregnant women and 520 maternal subjects and their infants) will be enrolled in this study.

Stage 1

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

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

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

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

Stage 2

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

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

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

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

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

The IRC will meet on an ad hoc and timely basis to review safety data if a stopping rule is triggered, and make recommendations for the study. In addition, the E-DMC will meet for regular review of accumulating safety data and for ad hoc review if a stopping rule is met.

At Visit 1, e-diaries will be used to collect systemic event data at baseline as well as prompted local reaction and systemic event data for 7 days after vaccination. In maternal subjects, the investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through Visit 3. At 1 week following delivery (Visit 5), the subject will be contacted by telephone to inquire about MAEs and SAEs, including hospitalizations, since

Visit 3. At all subsequent visits (Visits 6, 7, 8, and 9), only MAEs and SAEs, including hospitalizations, will be reported. In addition, AEs occurring up to 48 hours after the Visit 6 and 9 blood draws that are related to study procedures will also be reported.

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

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

In infant subjects, cord blood will be collected at delivery (blood may be collected in the infant subjects up to 72 hours after delivery if cord blood is unavailable) (Visit 1) and blood will be drawn at 6 and 14 weeks of age and 12 months of age (Visits 3, 4, and 7) for GBS6 antibody assessments. CCI [redacted]

CCI [redacted]

Stage 3

When Stage 2 maternal subjects and their infant subjects have completed the 6-week postdelivery/birth visit, safety and immunogenicity data will be unblinded by group, and analyzed and reviewed by the Pfizer IRC and the E-DMC. The IRC will select the GBS6 final dose and formulation to take into Stage 3 and further development.

Approximately 160 additional maternal subjects will be enrolled in Stage 3, to receive a single dose/formulation of the selected GBS6 or placebo (saline control) in a 1:1 ratio. There will be no dose escalation, no sentinel cohorts, and no planned stopping rules. The visit schedule, follow-up, and assessments for maternal subjects and their infant subjects will be similar to Stage 2. The additional data from Stage 3 will contribute to the safety database of maternal subjects to support the design the Phase 3 program.

Investigational Products

The investigational products are GBS6, composed of CPS of serotypes Ia, Ib, II, III, IV, and V, individually conjugated to CRM_{197} at dose levels of 5, 10, or 20 µg CPS/serotype/dose, formulated with or without $AlPO_4$, or placebo (saline control). At Visit 1, investigational

product will be administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm.

Statistical Methods

Statistical analyses will be descriptive in nature. All safety and immunogenicity data will be analyzed separately for nonpregnant women (Stage 1), maternal subjects (Stage 2 and Stage 3), and their infant subjects (Stage 2 and Stage 3). Safety and immunogenicity data from subjects who receive the same vaccine dose/formulation or placebo (saline control) in Stage 2 and Stage 3 (maternal subjects and their infant subjects) will be combined and analyzed together.

In addition, immunogenicity results from maternal subjects (Stages 2 and 3) and their infant subjects (Stages 2 and 3) may be analyzed together as appropriate.

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

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures (Section 6) and Assessments (Section 7) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Stage 1 – Schedule of Activities for Nonpregnant Women					
Visit Number	**0**	**1**	**2**	**3**	**4**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Telephone Contact**
Visit Window (Days)[a]	**Day -7 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**160-200 Days After Visit 1**
Informed consent	X				
Demography	X				
Medical history	X				
Vital signs[b]	X	X			
Physical examination	X				
HIV, HBV, and HCV testing (~5-mL blood sample)	X				
Urine pregnancy test		X			
Record nonstudy vaccine information	X	X	X	X	
Record concomitant medication	X	X	X	X	
Review inclusion and exclusion criteria	X				
Review screening laboratory results		X			
Contraception check[c]		X	X	X	X
Review temporary delay criteria		X			
Review continued eligibility		X	X	X	
Assign single subject identifier	X				
Assign subject randomization and container number		X			

Stage 1 – Schedule of Activities for Nonpregnant Women					
Visit Number	**0**	**1**	**2**	**3**	**4**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Telephone Contact**
Visit Window (Days)[a]	**Day -7 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**160-200 Days After Visit 1**
Blood draw (~15 mL per blood sample) for immunogenicity assessment[d]		X	X	X	
CCI					
Administer investigational product		X			
Postvaccination observation (30 minutes) and assessment of immediate adverse events		X			
Dispense e-diary, thermometer, and measuring device[e]		X			
Review and/or collect e-diary[f]		X	X		
Record adverse events	X	X	X	X	
Record medically attended adverse events and serious adverse events	X	X	X	X	X
CCI					

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

a. Day relative to the start of study vaccination (Day 1).
b. Vital signs include weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
c. The contraception check is an opportunity to confirm that contraception was/is used consistently and correctly.
C [redacted]
e. Subjects will record reactogenicity events in an e-diary each evening for 7 days following vaccination. Remind subjects that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary. Ask subjects to contact the investigator or site staff immediately if they are prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required.
f. Designated site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.
C [redacted]

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

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

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

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

a. Visits at 2 weeks and 1 month after vaccination will not be performed if delivery occurs before the visits. In that case, hematology and chemistry assessments due at the 2 week visit should be conducted at the delivery visit. Once delivery occurs, the visit windows are calculated based on delivery date.
b. If abnormal laboratory values (as defined in Screening, Section 6.2.1, and in Section 7.5.3) are reported at Visit 0/Visit 2 and the investigator believes the results to be erroneous, the abnormal laboratory parameters may be retested.
c. Vital signs include weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
[redacted]
e. Blood sample and rectal/vaginal swabs may be collected up to 72 hours after delivery.
f. Subjects will provide (in an e-diary) a baseline assessment of prompted systemic events prior to vaccination and subjects will record (in an e-diary) reactogenicity events each evening for 7 days following vaccination. Remind subjects that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary. Ask subjects to contact the investigator or site staff immediately if they are prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required (see Section 6.4).
g. Designated site staff will review e diary data online at frequent intervals for the 7 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.
h. Only adverse events occurring up to 48 hours after each blood draw that are related to study procedures must be recorded in the case report form.
[redacted]

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

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

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

1. INTRODUCTION

1.1. Indication

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

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

1.2. Background and Rationale

1.2.1. Disease Overview

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

1.2.2. GBS Disease in Infants and Pregnant Women

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

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

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

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

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

In other countries, such as in certain European countries, where interventions are less widely used or a risk-based approach is used, the trend in incidence rates may be unchanged or increasing slightly.[6,26] Neither approach has eliminated GBS disease in infants. Furthermore, many countries around the world do not have the resources to implement IAP.

Even with potential underreporting, the highest rates of GBS disease are found in LMICs,[15] where healthcare access and standards of prenatal care may vary, or the resources for significant preventive interventions are not available.

1.2.3. Rationale for Development of GBS6

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

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

1.2.3.2. Maternal Antibody and Protection Against GBS Disease in Infants

During the third trimester of pregnancy, only IgG antibodies are actively transported across the placenta. This provides a means for protective antibody to be transferred from a mother to her newborn.[34] The efficiency of antibody transfer depends on placental integrity, maternal total IgG, GA at delivery, and IgG subclass (the immunoglobulin G1 [IgG1] subclass is most efficiently transferred).[28] Researchers measured antibody in sera collected at delivery from GBS-colonized mothers whose infants had developed EOD, and in GBS-colonized women whose infants had not developed EOD. There was a correlation between low maternal antibody concentration to serotype III (as measured in an IgG assay) and infant susceptibility to EOD due to serotype III.[35] Since the initial study, additional work was conducted demonstrating the correlation between serotype Ia–specific anti–capsular polysaccharide (CPS) antibody in the mother and protection of the baby against GBS EOD due to serotype Ia, and a directional effect with the serotype V antibody.[36-39] This suggests that anti-CPS antibody protects against GBS disease, a mechanism similar to that exploited against other encapsulated organisms, and the antibody is transported across the placenta. These findings support the biological plausibility that increasing the levels of maternal anti-CPS IgG antibody by vaccination of pregnant women with serotype-specific

polysaccharide conjugate antigens will increase the proportion of women with potentially protective levels of IgG and will result in placental transfer of protective antibody to a large number of infants.

1.2.3.3. Clinical Experience With Polysaccharide Conjugate Vaccines and GBS Polysaccharide Conjugate Vaccine

There is significant experience with the use of polysaccharide conjugate vaccines to prevent disease due to encapsulated bacteria in infants, children, and adults.[40,41] A number of polysaccharide conjugate vaccines have been developed and globally licensed by Pfizer (HibTITER®, Meningitec®, Prevenar®, Prevenar 13®) and other vaccine manufacturers (eg, Menveo, ActHIB, Hiberix). These vaccines have a well-established safety profile and induce high levels of functionally active antibodies that are protective as demonstrated either through efficacy studies or based on established immune correlates of protection.

Investigational GBS polysaccharide conjugate vaccines have been evaluated in clinical trials in pregnant women, including a trivalent (Ia, Ib, and III) GBS CPS–cross-reactive material 197 (CRM_{197}) conjugate vaccine in South Africa.[42,43] These studies demonstrated the acceptable safety profile of GBS polysaccharide conjugate vaccines, as well as the induction of immune responses to the GBS vaccine serotypes in their infants.

1.2.4. Group B Streptococcus 6-Valent Polysaccharide Conjugate Vaccine

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

The GBS6 candidates are composed of polysaccharides of the 6 most prevalent serotypes causing >95% of GBS disease in infants, individually conjugated to the CRM_{197} carrier protein. They contain 5, 10, or 20 μg CPS/serotype/dose, and are formulated with or without aluminum phosphate ($AlPO_4$). Refer to Table 3 for further details. The candidates have been developed based on Pfizer historical experience with licensed and investigational polysaccharide conjugate vaccines, published/public data with other investigational GBS polysaccharide conjugate vaccines, and data from the preclinical models of GBS6.[41,44-52]

The CPS/serotype/dose is within the range clinically evaluated in monovalent and multivalent vaccines of GBS polysaccharide conjugated to tetanus toxoid or CRM_{197}.[45,53,54] These investigational vaccines have also been evaluated in pregnant women in clinical studies, with no safety concerns identified to date. Preclinical data show that GBS6 induces serotype-specific IgG responses and opsonophagocytic activity (OPA) that are protective against an infectious challenge in the offspring in animal models.

The formulations with $AlPO_4$ may offer particular advantages in immune response based on their potential to drive an IgG1 antibody response, which is the antibody subclass preferentially transported across the placenta.[55,56] Therefore, GBS6 formulated with $AlPO_4$ is being assessed in early clinical development to determine the optimal formulation that induces maximally protective antibody levels in humans.

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

1.2.5. Study Rationale

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

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

Stage 2 will commence following a review of the 1-month postvaccination safety data from the Phase 1/2 LMIC Stage 1 cohort and 1-month postvaccination safety and immunogenicity data from the Phase 1/2 FIH study (C1091001). If the safety and immunogenicity profile is deemed acceptable, the safety, tolerability, and immunogenicity of 3 ascending dose levels (5, 10, or 20 µg CPS/serotype/dose) of GBS6 formulated with or without $AlPO_4$ will be assessed when administered as a single dose to healthy pregnant women aged 18 to 40 years during their 27 to 36 weeks of pregnancy. Of note, all 3 dose levels (5, 10, or 20 µg CPS/serotype/dose) may not be evaluated during Stage 2 should any dose/formulation level be deemed unacceptable after review of immunogenicity data from the Phase 1/2 FIH study (C1091001) and the safety data from Stage 1 of the C1091002 study.

Stage 2 will use sentinel cohorts to assess safety to allow progression to the next higher dose. These sentinel cohorts serve as a Phase 1 evaluation in the study based on the small number of subjects in the cohort and the focus on safety, including safety laboratory assessments. Enrollment of the remaining cohorts serves as the Phase 2 component of the study and will provide an increased number of maternal subjects for immunogenicity assessment as well as expand the safety data set. Safety and GBS6 antibody transfer to infants born from vaccinated women will be evaluated. A single dose and formulation for further evaluation in Stage 3 of the study will be selected after review of the 6-week postdelivery safety and immunogenicity data from maternal subjects and their infant subjects. In Stage 3, an additional cohort of healthy pregnant women will be enrolled to receive the selected GBS6 dose/formulation to provide an expanded safety and immunogenicity data set (both pregnant women and their infant subjects) and to support progression of the development of this vaccine.

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

CCI [redacted]

CCI [redacted]

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives and Endpoints

2.1.1. Primary Objective: Stage 1

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

2.1.2. Primary Endpoints: Stage 1

- Proportions of nonpregnant women reporting prompted local reactions within 7 days following administration 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 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 investigational product.

- Proportions of nonpregnant women reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) through 6 months following administration of investigational product.

2.1.3. Primary Objectives: Stage 2

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

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

2.1.4. Primary Objectives: Stage 3

- To describe the safety and tolerability of 1 selected dose/formulation of GBS6 when administered to healthy pregnant women 18 to 40 years of age vaccinated at 27 to 36 weeks' gestation.

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

2.1.5. Primary Safety Endpoints (Maternal Subjects): Stages 2 and 3

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

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

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

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

2.1.6. Primary Safety Endpoints (Infant Subjects): Stages 2 and 3

- Proportions of infant subjects with specific birth outcomes.

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

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

2.2. Secondary Objectives and Endpoints

2.2.1. Secondary Objective: Stage 1

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

2.2.2. Secondary Objective: Stage 2

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

2.2.3. Secondary Objective: Stage 3

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

2.2.4. Secondary Objectives: Stages 2 and 3

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

2.2.5. Secondary Endpoints: Stage 1

- GBS serotype-specific IgG geometric mean concentrations (GMCs) 1 month after vaccination in nonpregnant women.
- GBS serotype-specific OPA geometric mean titers (GMTs) measured 1 month after vaccination in nonpregnant women.

2.2.6. Secondary Endpoints (Maternal Subjects): Stages 2 and 3

- GBS serotype-specific IgG GMCs measured at 2 weeks and 1 month after vaccination and at delivery in maternal subjects.
- GBS serotype-specific OPA GMTs measured at 2 weeks and 1 month after vaccination and at delivery in maternal subjects.

2.2.7. Secondary Endpoints (Infant Subjects): Stages 2 and 3

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

CCI [redacted]

[redacted]

3. STUDY DESIGN

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of a multivalent GBS vaccine in healthy 18- to 40-year-old nonpregnant women and pregnant women vaccinated between 27 0/7 and 35 6/7 weeks' gestation and their infant subjects.

3.1. Stage 1

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

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

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

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

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

- enrollment in the sentinel cohort for the next higher dose level (see Table 2).

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

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

In addition to the ad hoc meetings convened in the case a stopping rule is met, the E-DMC will also meet periodically to conduct routine reviews of safety data.

3.3. Stage 3

When Stage 2 maternal subjects and their infant subjects have completed the 6-week postdelivery/birth visit, safety and immunogenicity data will be unblinded by group, analyzed, and reviewed by the Pfizer IRC and E-DMC. The IRC will select the GBS6 final dose and formulation to take into Stage 3 and further development.

Approximately 160 additional maternal subjects will be enrolled into Stage 3, to receive a single dose/formulation of the selected GBS6 or placebo (saline control) in a 1:1 ratio. There will be no dose escalation, no sentinel cohorts, and no planned stopping rules. The visit schedule, follow-up, and assessments for maternal subjects and their infant subjects will be similar to those in Stage 2. The additional data from Stage 3 will contribute to the safety database of maternal subjects to support the design of the Phase 3 program.

Table 1. Enrollment and Dose Escalation Design

<table>
<tr><th colspan="2">Dose Escalation</th><th>Stage 1
Nonpregnant
Women</th><th>Stage 1 Safety Data Review by Pfizer IRC and E-DMC[a]</th><th colspan="6">Stage 2
Maternal Subjects</th><th>Stage 2 Safety and Immunogenicity Review/Dose Selection</th><th>Stage
3 Maternal
Subjects</th></tr>
<tr><td rowspan="3">Lowest Dose</td><td rowspan="3">- GBS6 lowest dose with $AlPO_4$
- GBS6 lowest dose without $AlPO_4$
- Placebo (saline control)</td><td rowspan="3"></td><td rowspan="3"></td><td>Enroll sentinel cohort (n=42)</td><td>14-Day safety review by IRC</td><td colspan="2">Complete enrollment of expanded[b] cohort(n=78)</td><td colspan="2" rowspan="3"></td><td rowspan="3"></td><td rowspan="3">Enroll and vaccinate (n=160, GBS6 selected[c] or placebo (saline)</td></tr>
<tr><td colspan="2" rowspan="2"></td><td>Enroll sentinel cohort[b] (n=42)</td><td>14-Day safety review by IRC</td></tr>
<tr><td colspan="2">Complete enrollment of expanded cohort[b] (n=78)</td></tr>
<tr><td rowspan="3">Middle Dose</td><td rowspan="3">- GBS6 middle dose with $AlPO_4$
- GBS6 middle dose without $AlPO_4$
- Placebo (saline control)</td><td rowspan="3"></td><td colspan="3" rowspan="3"></td><td colspan="2" rowspan="3"></td><td rowspan="3"></td></tr>
<tr><td colspan="2" rowspan="2"></td></tr>
<tr><td rowspan="2"></td></tr>
<tr><td rowspan="3">Highest Dose</td><td rowspan="3">- GBS6 highest dose with $AlPO_4$
- GBS6 highest dose without $AlPO_4$
- Placebo (saline control)</td><td rowspan="3">Enroll and vaccinate[d] (n=66)</td><td rowspan="3"></td><td colspan="4" rowspan="3"></td><td rowspan="3"></td><td rowspan="3"></td></tr>
<tr><td rowspan="2"></td></tr>
<tr><td rowspan="2"></td></tr>
<tr><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3"></td><td>Enroll sentinel cohort[b] (n=42)</td><td>14-Day safety review by IRC</td><td>Complete enrollment of expanded cohort (n=78)</td><td rowspan="3"></td><td rowspan="3"></td></tr>
<tr><td colspan="3" rowspan="2"></td></tr>
<tr><td rowspan="2"></td></tr>
</table>

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

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

3.4. Duration of Subject Participation

Each subject will participate in the study for approximately 6 months for Stage 1 (nonpregnant women) and up to 16 months for Stages 2 and 3 (pregnant women and their infant subjects).

3.5. Duration of Study

The study duration will be approximately 48 months.

3.6. Number of Subjects

Refer to Table 2 below for a detailed description of the number of subjects per stage and dose/formulation group. Subjects who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal. A total of approximately 586 subjects (66 nonpregnant women and 520 maternal subjects and their infant subjects) will be enrolled in this study by central randomization.

3.6.1. Stage 1

Approximately 66 subjects (nonpregnant women) will be enrolled into Stage 1, 22 subjects at each formulation of GBS6 (with/without $AlPO_4$) and 22 subjects in the placebo group.

3.6.2. Stage 2

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

3.6.3. Stage 3

Approximately 160 maternal subjects will be enrolled into Stage 3, 80 at the selected GBS6 dose/formulation and 80 in the placebo group.

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

Stage 1 Dose/Formulation Group		Total (1:1:1)		
Highest Dose[a]	GBS6 (20 µg CPS/serotype/dose) with $AlPO_4$	22		
	GBS6 (20 µg CPS/serotype/dose) without $AlPO_4$	22		
	Placebo (saline control)	22		
Stage 2 Dose/Formulation Groups		**Sentinel (1:1:1)**	**Expanded (1:1:1)**	**Total**
Lowest Dose	GBS6 lowest dose with $AlPO_4$	14	26	40
	GBS6 lowest dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[b]
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[b]
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[b]
Stage 3 Dose/Formulation Group		**Total (1:1)**		
Selected Dose	Selected GBS6 dose/formulation	80		
	Placebo (saline control)	80		

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

a. One hundred four healthy adults (males and females) aged 18 to 49 years have received this dose level (~52/formulation with/without $AlPO_4$) in the US FIH Phase 1/2 study (C1091001).

b. Approximately 120 pregnant control subjects receiving placebo (saline control) in total in Stage 2.

4. SUBJECT ELIGIBILITY CRITERIA

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

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria – Stage 1

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

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

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

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

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

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

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

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

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

   c. Have medically confirmed ovarian failure.

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

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

4.2. Exclusion Criteria – Stage 1

Subjects with any of the following characteristics/conditions will not be included in the study:

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

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

3. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

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

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

6. Immunocompromised subjects with known or suspected immunodeficiency.

7. Subjects who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt through the 1-month postvaccination blood draw. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, subjects should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 30 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

9. Any known or suspected autoimmune or neuroinflammatory disease.

10. Current alcohol abuse or illicit drug use.

11. Previous vaccination with any licensed or investigational GBS vaccine, or planned receipt during the subject's participation in the study (through the last blood draw).

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

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

14. Female subjects who are breastfeeding.

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

4.3. Inclusion Criteria – Stages 2 and 3 – Maternal Subjects

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

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

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

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

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

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

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

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

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

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

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

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

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

      - If there is a discrepancy of >21 days between the LMP-determined GA and the third-trimester ultrasound OR if the LMP is uncertain/unknown, then the GA should be determined using the third-trimester ultrasound.

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

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

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

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

4.4. Exclusion Criteria – Stages 2 and 3 – Maternal Subjects

Subjects with any of the following characteristics/conditions will not be included in the study:

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

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

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

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

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

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

7. Current alcohol abuse or illicit drug use.

8. Body mass index (BMI) of ≥40 kg/m2 at the time of the screening visit.

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

10. Subjects with known or suspected immunodeficiency.

11. Subjects who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt through the postvaccination blood draw. If systemic corticosteroids have been

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

12. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

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

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

15. Vaccination with diphtheria- or CRM_{197}-containing vaccine, from 6 months before investigational product administration.

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

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

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

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

19. Any known or suspected autoimmune or neuroinflammatory disease.

4.5. Inclusion Criteria – Infant Subjects – Stages 2 and 3

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

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

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

4.6. Exclusion Criteria – Infant Subjects – Stages 2 and 3

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

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

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

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

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

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

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

4.8. Lifestyle Requirements

4.8.1. Contraception (Stage 1 Subjects Only)

All female subjects who are of childbearing potential and are sexually active with 1 or more members of the opposite sex must agree to use a highly effective method of contraception consistently and correctly for at least 3 months after administration of investigational product. The investigator or his or her designee, in consultation with the subject, will

confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the schedule of activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

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

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

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

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

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

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

4.9. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the

established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. INVESTIGATIONAL PRODUCTS

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

For this study, the investigational product(s) are GBS6 (containing 5, 10, or 20 µg CPS/serotype/dose, each formulated with or without $AlPO_4$) and placebo (saline control). Subjects will receive 1 dose of either GBS6, with or without $AlPO_4$, or placebo (saline control) at Visit 1 administered intramuscularly by CCI [redacted], preferably of the nondominant arm. The dose level/formulation received by each subject will be based on which stage of the study the subject will be enrolled in (see Table 1).

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

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

5.1. Investigational Product Supplies

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

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

5.1.1. Dosage Form(s) and Packaging

GBS6 is composed of serotypes Ia, Ib, II, III, IV, and V CPS CCI [redacted] There are 3 dose levels (5, 10, or 20 µg CPS/serotype/CCI [redacted]), each formulated either with $AlPO_4$, CCI [redacted], or without $AlPO_4$. See Table 3 for further details.

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

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

5.1.2. Preparation and Dispensing

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

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

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

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

5.2. Allocation to Investigational Product

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

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

Stage 1 subjects and maternal subjects (Stages 2 and 3) will be allocated to an investigational product group as described above. Infants (infant subjects) of the maternal subjects will be assigned a subject number at birth.

5.3. Subject Compliance

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

5.4. Administration

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

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

Investigational product administration details will be recorded on the case report form (CRF).

In Stage 1, subjects will receive 1 dose of either GBS6, formulated with or without $AlPO_4$, or placebo (saline control) at Visit 1 in accordance with the study's schedule of activities. Stage 2 subjects will receive 1 of 3 possible dose levels of GBS6, formulated with or without $AlPO_4$, or placebo (saline control) at Visit 1 in accordance with the study's schedule of activities. In Stage 3, subjects will receive 1 selected dose/formulation of either GBS6 or placebo (saline control) at Visit 1 in accordance with the study's schedule of activities.

GBS6 or placebo (saline control) should be administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm.

5.5. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. Investigational products should be stored in their original containers and in accordance with the labels.

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

The unblinded dispenser/administrator will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

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

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

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer. Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. CCI [redacted]

5.6. Investigational Product Accountability

The unblinded dispenser/administrator at the investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Blinding of the Site Personnel

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

5.8. Blinding of the Sponsor

In each stage of the study, sponsor study team members will remain blinded to vaccine assignment of all subjects enrolled in that stage, following the principles outlined in ICH E9 guideline on Statistical Principles for Clinical Trials, Section 2.3.1,[57] until the planned interim analysis in that stage. Three unblinded interim analyses (Section 9.4) are planned in each stage of the study: Stage 1, Stage 2, and Stage 3. In an event that unblinded results need to be submitted for regulatory communications prior to study team unblinding, efforts will be made to ensure study team members involved in subject assessments are blinded.

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

5.9. Breaking the Blind

The study will be subject and investigator blinded.

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

5.10. Concomitant Treatment(s)

5.10.1. Prohibited Nonstudy Vaccines and Medications During the Study

5.10.1.1. Stage 1

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

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

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

5.10.1.2. Stages 2 and 3 – Maternal Subjects

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

- Nonstudy diphtheria- and CRM_{197}-containing vaccines, blood/plasma products or immunoglobulins (except anti-D immunoglobulin, eg, RhoGAM, which can be given at any time), and immunosuppressive therapy are prohibited during the course of the study.

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

5.10.2. Permitted Nonstudy Vaccines and Medications During the Study

5.10.2.1. Stage 1

- Licensed influenza vaccine may be given during the study starting 15 days after investigational product administration. If medically necessary (eg, pandemic), influenza vaccine may be given at any time.

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

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

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

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

5.10.2.2. Stages 2 and 3 – Maternal Subjects

- Licensed influenza vaccine, and tetanus vaccines may be given during the study starting 15 days after investigational product administration as per local recommendation for immunization in pregnant women. If medically necessary (eg, pandemic), influenza vaccine may be given at any time.

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

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

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

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

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

5.10.2.3. Stages 2 and 3 – Infant Subjects

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

5.10.3. Recording Nonstudy Vaccinations and Concomitant Medications

5.10.3.1. Stage 1

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

Any medications taken from the signing of ICD through Visit 3 (1-month follow-up visit) will be recorded in the CRF. Additionally, any medication taken to treat AEs from the signing of the ICD through Visit 4 will be recorded in the CRF.

5.10.3.2. Stages 2 and 3 – Maternal Subjects

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

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

5.10.3.3. Stages 2 and 3 – Infant Subjects

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

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

6. STUDY PROCEDURES

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

6.1. Stage 1 Study Procedures – Nonpregnant Women

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

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

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

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Assign a single subject identifier using the IRT system.
- Obtain and record the subject demography (including date of birth, sex, race, and ethnicity).
- Obtain and record any medical history of clinical significance.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 4).
- Obtain a blood sample (approximately 5 mL) for HIV, HBV, and HCV testing. Subjects testing positive for HIV, acute or chronic HBV, or HCV will not be eligible for randomization.
- Complete the source documents.
- Record nonstudy vaccinations and medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.1.2. Visit 1 – Vaccination (Day 1)

- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in Section 6.5, and meets none of the temporary delay criteria as described in Section 4.7.
- Review screening laboratory results.
- Prior to vaccination, measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.

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

- Prior to vaccination, collect a blood sample of approximately 15 mL for immunogenicity assessments.

[redacted]

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

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

- The unblinded administrator administers a single 0.5-mL injection of investigational product into the deltoid muscle, preferably of the nondominant arm.

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

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

- Issue the subject an e-diary and provide instructions on its completion. Ask the subject to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

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

- Remind subjects that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary.

- Ask the subject to contact the site staff or investigator if a medically attended event (eg, emergency room) or hospitalization occurs.

- Complete the subject's source documents.
- Record nonstudy vaccinations and concomitant medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF and an unblinded site staff member updates the investigational product accountability records.
- Designated site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.

6.1.3. Visit 2 – 2-Week Follow-up Visit (14-17 Days After Visit 1)

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- [redacted]
- Review the subject's e-diary data and collect the e-diary. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Complete the subject's source documents.
- Record nonstudy vaccinations and medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.1.4. Visit 3 – 1-Month Follow-up Visit (28-42 Days After Visit 1)

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.

[redacted]

- Complete the subject's source documents.
- Record nonstudy vaccinations and concomitant medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

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

- Verify understanding of and compliance with protocol requirements for contraception.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.2. Stage 2 and 3 Study Procedures – Maternal Subjects

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

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

For Stage 2 sentinel-cohort subjects only: In the 14-day screening period, retesting of the screening blood/chemistry laboratory parameters will be allowed at the discretion of the investigator if the investigator believes the results to be erroneous. In this circumstance, subjects will return for a second screening visit within the 14-day screening period to reevaluate the screening laboratory parameters (see Section 6.2.2).

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

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Assign a single subject identifier using the IRT system.
- Obtain and record the subject demography (including date of birth, sex, race, and ethnicity).
- Obtain and record current alcohol and tobacco usage.
- Obtain and record any medical and obstetric history of clinical significance including history from prior and current pregnancy(ies). Refer to the SRM for further details.
- Record the last normal menstrual period (LMP) and estimated date of delivery (EDD).
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Perform obstetric examination including but not limited to scars from previous deliveries, fundal height, fetal heart tones, and fetal movement.
- Perform obstetric ultrasound and record findings.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 4).
- Obtain blood sample (approximately 10 mL) for HBV, HCV, HIV, and syphilis testing. Subjects testing positive for HIV, acute or chronic HBV, HCV, or syphilis will not be eligible for randomization.
- Stage 2 sentinel cohort only: Obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments. The following parameters will be assessed:
    - Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelets.

  - Blood chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.

- Obtain urine sample for glucose and protein testing (urine dipstick).
- Complete the source documents.
- Record nonstudy vaccinations and medications (including antibiotic medications) as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

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

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 4).
- Obtain a blood sample (approximately 10 mL) for analysis of hematology and blood chemistry assessments (see Section 7.5.3). Retest only abnormal laboratory parameters from Visit 0.
- Complete the source documents.
- Record nonstudy vaccinations and medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

6.2.3. Visit 1 – Vaccination (Day 1) Visit

- Review laboratory results.

- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in Section 6.5, and meets none of the temporary delay criteria as described in Section 4.7.

- Prior to vaccination, measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.

- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.

- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.

- Obtain urine sample for glucose and protein testing (urine dipstick).

- Issue the subject an e-diary and provide instructions on its completion. Ensure that the subject records a baseline assessment of prompted systemic events in the e-diary prior to vaccination.

- Prior to vaccination, collect a blood sample of approximately 15 mL for immunogenicity assessments.

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

- The unblinded administrator administers a single 0.5-mL injection of investigational product into the deltoid muscle, preferably of the nondominant arm.

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

- Issue a measuring device to measure local reactions and a digital thermometer for recording daily temperatures, and provide instructions on their use.
- Ask the subject to complete the e-diary from Day 1 to Day 7 (Day 1 is the day of vaccination).
- Ask the subject to contact the site staff or investigator immediately if prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring ≥21 measuring device units [≥10.5 cm]).
- Remind subjects that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary.
- Ask the subject to contact the site staff or investigator if a medically attended event (eg, emergency room) or hospitalization occurs.
- Complete the subject's source documents.
- Record nonstudy vaccinations and concomitant medications (including antibiotic medications) as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF and an unblinded site staff member updates the investigational product accountability records.
- Designated site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.

6.2.4. Visit 2 – 2-Week Follow-up Visit (14-17 Days After Visit 1)

If delivery occurs before this visit, this visit will not be conducted; however, the hematology and chemistry assessments planned to be collected at this visit should be conducted at the delivery visit, if possible. For the other procedures to be conducted at delivery, see Section 6.2.6.

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate

worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.

- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- **Stage 2 sentinel cohort only:** Obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments. The following parameters will be assessed:
  - Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, and platelets.
  - Blood chemistries: ALT, AST, alkaline phosphatase, total bilirubin, BUN, and creatinine.
  - Retesting of abnormal laboratory parameters will be allowed at the discretion of the investigator if the investigator believes the results to be erroneous.
- Review the subject's e-diary data and collect the e-diary. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Complete the subject's source documents.
- Record nonstudy vaccinations and concomitant medications (including antibiotic medications) as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.2.5. Visit 3 – 1-Month Follow-up Visit (28-42 Days After Visit 1)

If delivery occurs before this visit, please conduct the delivery visit instead. For procedures to be conducted at delivery, see Section 6.2.6.

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or

complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.

- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.

[redacted]

- Complete the subject's source documents.
- Record nonstudy vaccinations and medications (including antibiotic medications) as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.2.6. Visit 4 – Delivery

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Record nonstudy vaccinations and antibiotic medications as described in Section 5.10.3.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments. The blood sample may be collected up to 72 hours after delivery. Refer to the SRM for blood sample collection guidelines.

[redacted]

- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record pregnancy outcome information.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5. This telephone contact should be performed by the investigator or a medically qualified member of the study site staff.
- Complete the subject's source documents.
- Record antibiotic medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.2.8. Visit 6 – 6-Week Postdelivery Follow-up (35-49 Days After Delivery)

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.

[redacted].

- Complete the subject's source documents.
- Record antibiotic medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Complete the subject's source documents.
- Record antibiotic medications as described in Section 5.10.3.

- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Complete the subject's source documents.
- Record antibiotic medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- Complete the subject's source documents.
- Record antibiotic medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.3. Stage 2 and 3 Study Procedures – Infant Subjects

6.3.1. Visit 1 – Delivery

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Assign a single subject identifier using the IRT system.
- Collect demography (including date of birth, sex, race, and ethnicity) and birth information, including but not limited to infant subject vital status (live, stillbirth, neonatal death), appearance, pulse, grimace, activity, and respiration (Apgar) score, birth length, birth weight, head circumference, and Ballard score.
- Measure vital signs, including axillary temperature, pulse rate, and respiratory rate.

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

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

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

[redacted]

- Complete the subject's source documents.

- Record AEs as described in Section 7.8 and Section 8.

- Record nonstudy vaccines and concomitant medications (including antibiotic medications) as described in Section 5.10.3.

- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.

- Collect and record breastfeeding information.

- Complete the subject's source documents.

- Record AEs as described in Section 7.8 and Section 8.

- Record nonstudy vaccines and concomitant medications (including antibiotic medications) as described in Section 5.10.3.

- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.

- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.

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

- Collect a blood sample of approximately 5 mL for immunogenicity assessments. Refer to the SRM for blood sample collection guidelines.

- [redacted]

- Collect and record breastfeeding information.

- Complete the subject's source documents.

- Record AEs as described in Section 7.8 and Section 8.

- Record nonstudy vaccines and concomitant medications (including antibiotic medications) as described in Section 5.10.3.

- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.

- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.

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

- Collect a blood sample of approximately 5 mL for immunogenicity assessments. Refer to the SRM for blood sample collection guidelines.

- [redacted]

- Collect and record breastfeeding information.

- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines and antibiotic medications as described in Section 5.10.3.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Collect a blood sample of approximately 5 mL for assessment of antibody responses to routine pediatric vaccines. Refer to the SRM for blood sample collection guidelines.
- Collect and record breastfeeding information.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines and antibiotic medications as described in Section 5.10.3.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Collect and record breastfeeding information.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.

- Record nonstudy vaccines and antibiotic medications as described in Section 5.10.3.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Collect a blood sample of approximately 5 mL for immunogenicity assessments and assessment of antibody responses to routine pediatric vaccines. Refer to the SRM for blood sample collection guidelines.
- Collect and record breastfeeding information.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines and antibiotic medications as described in Section 5.10.3.
- The investigator or an authorized designee completes the CRF.

6.4. Unscheduled Visit (Stages 1, 2, and 3 – Maternal Subjects)

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

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

- The investigator determined it was not needed.

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

If the subject is unable to attend the unscheduled visit, any ongoing reactions must be assessed at the next scheduled visit.

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

- Measure oral temperature.
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess any injection site pain that is present in accordance with the grading scale provided in Section 7.5.2.
- Assess for lymphadenopathy associated with any present local reaction.
- Assess any systemic events (nausea/vomiting, diarrhea, headache, fatigue, muscle pain, or joint pain) that are present in accordance with the grading scale provided in Section 7.5.2.

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

Subjects will also be instructed to contact site staff if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for headache, fatigue, muscle pain, joint pain, etc) within 7 days after vaccination. Study staff may contact the subject to obtain additional information on Grade 3 events entered into the e-diary. Lastly, subjects will be instructed to contact the site to report any significant illness, medical event, or hospitalization that occurs during the study period. The site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

6.5. Subject Withdrawal

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

considered for withdrawal from study procedures for any medical condition(s) that, in the opinion of the investigator, would contraindicate blood sampling.

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

6.5.1. Withdrawal of Consent

After investigational product administration at Visit 1, subjects (nonpregnant women in Stage 1; maternal subjects, and parents of infant subjects born to maternal subjects in Stages 2 and 3) who request to discontinue further study procedures (eg, blood draws) at upcoming visits will be asked to remain in the study for protocol-specified safety follow-up procedures. The only exception to this is when a subject or parent specifically withdraws consent for any further contact. It is permissible that Visit 4 (Stage 1 subjects), Visit 9 (Stage 2 and 3 maternal subjects), and Visit 7 (Stage 2 and 3 infant subjects) be conducted via telephone contact for subjects who are staying in the study for protocol-specified safety follow-up procedures only. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further study procedures (eg, blood draws) and/or postvaccination study safety follow-up, and entered on the appropriate CRF page.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject or parents after a minimum of 2 documented phone calls, faxes, or emails as well as lack of response by the subject or subject's parent to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the

inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

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

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

7. ASSESSMENTS

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

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

7.1. Pregnancy Testing (Applicable to Stage 1 Subjects Only)

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of investigational product. A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study. In the case of a positive confirmed pregnancy *after* administration of investigational product, the subject may remain in the study for blood sample collections and safety monitoring.

7.2. Biological Samples

Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity.

Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the subject's genetic material will be performed.

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

7.3. Immunogenicity

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

7.3.1. GBS Antibody Testing

Sera collected from nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) throughout the study and from infant subjects at birth and at 6 weeks, 14 weeks, and 12 months of age will be assayed for GBS6 serotype-specific anticapsular antibodies. Sample collection, processing, storage, and shipping information can be found in the SRM or equivalent manual. OPA results for the 6 serotypes (Ia, Ib, II, III, IV, and V) will be determined in all subjects for each blood sample. Results will be reported as OPA titers. Concentrations of anticapsular IgG for the 6 serotypes (Ia, Ib, II, III, IV, and V) will be determined in all subjects for each blood sample by direct Luminex immunoassay (dLIA) and reported as IgG concentrations. CCI [redacted]

CCI [redacted]

7.3.3. Assessment of Antibody Responses to Routine Pediatric Vaccines in Infant Subjects

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

CCI [redacted]

[redacted]

[redacted]

7.5. Safety Parameters

Safety parameters will be assessed as described in the schedule of activities, Section 6, and below.

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

The safety parameters include e-diary reports of local reactions and systemic events that occur in the 7 days after investigational product administration. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 7.5.2.

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

In addition, AEs, MAEs, and SAEs are collected, recorded, and reported as defined in Section 8.

7.5.1. Subject Electronic Diary

The subject will be asked to monitor and record local reactions, systemic events, including fever, and antipyretics/pain medication used to prevent and/or treat symptoms, each evening for 7 days following vaccination (where Day 1 is the day of vaccination) on a system that

uses a personal digital assistant (PDA) or other technology. In Stages 2 and 3, a baseline assessment (nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, or joint pain over the previous month) prior to vaccination will be recorded in the e-diary. This system, hereafter referred to as the subject's e-diary, allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Data on local reactions, systemic events, and antipyretics/pain medication used to prevent and/or treat symptoms reported on the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting. These data do not need to be reported by the investigator in the CRF. However, if a subject withdraws because of prompted events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

Investigators (or appropriately qualified designee) are required to review the e-diary data online to evaluate subject compliance and as part of the ongoing safety review (see Stopping Rules in Section 7.7).

The investigator or designee must contact the subject in order to obtain stop dates for any reactions ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

7.5.2. Grading Scale for Prompted Events

The grading scales used in this study to assess AEs as described below are based on concepts outlined in the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[58]

7.5.2.1. Local Reactions

From Day 1 to Day 7, where Day 1 is the day of vaccination, subjects will be asked to assess pain at the injection site, redness, and swelling and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21+), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 4 below. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the subject as mild, moderate, or severe according to the grading scale in Table 4 below. A subject 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 subject's local reaction as Grade 4, after physical examination of the subject 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 subject. If a subject experiences a Grade 4 local reaction, the

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

If a local reaction persists beyond the end of the e-diary period following vaccination, the subject will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Table 4. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Grade 4[b]
Pain at injection site	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity[c]	Emergency room visit or hospitalization
Erythema/ Redness	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Induration/ Swelling	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

a. Subjects experiencing ≥ Grade 3 local reactions are to be seen by the study site.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the electronic diary but will be recorded as an AE on the case report form.
c. Prevents daily activity, ie, results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

7.5.2.2. Systemic Events

In Stages 2 and 3, prior to vaccination, on Day 1, a baseline assessment (nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain over the previous month) will be recorded in the e-diary. From Day 1 to Day 7, where Day 1 is the day of vaccination, subjects will be asked to assess nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the subject as mild, moderate, or severe according to the grading scale in Table 5 below. Subjects will also be instructed to contact site staff if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, or joint pain) within 7 days after vaccination. Study staff may also contact the subject to obtain additional information on Grade 3 events entered into the e-diary.

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

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

Table 5. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

a. Subjects experiencing ≥ Grade 3 systemic events are to be seen by the study site.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the electronic diary but will be collected as an AE on the case report form.
c. Prevents daily routine activity, ie, results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

7.5.2.3. Fever

In order to record information on fever, a digital thermometer will be given to the subject with instructions on how to measure oral temperature at home. Temperature will be collected in the evening daily for 7 days following vaccination (where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature less than 100.4°F [38.0°C] in order to collect a stop date in the CRF). A subject with a fever >104.0°F (>40.0°C) will be prompted to contact the investigator to assess the fever and perform an unscheduled visit as appropriate.

Study staff must also contact the subject to obtain additional information if a temperature of >102°F is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 6 below:

Table 6. Ranges for Fever

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

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

7.5.3. Laboratory Tests

For Stage 2 sentinel-cohort subjects, the safety laboratory tests in Table 7 will be performed at times defined in the schedule of activities and Section 6 of the protocol.

Table 7. Laboratory Tests

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

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

A toxicity grading scale adapted for use in pregnant women will be used to grade laboratory test abnormalities.[59] Please refer to the SRM for further details.

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

7.6. Use of Antipyretic/Pain Medication

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

7.7. Stopping Rules

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7.8. Other Safety Monitoring

7.8.1. Adverse Events

AEs and SAEs reported outside of the e-diary are recorded and reported as described in Section 8.

7.8.2. Immediate Adverse Events

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

7.8.3. Medically Attended Adverse Events

MAEs will be assessed from screening for all subjects up to Visit 4 (Stage 1) for nonpregnant subjects, up to Visit 9 for maternal subjects (Stages 2 and 3), and up to Visit 7 for infant subjects (Stages 2 and 3).

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

7.8.4. Adverse Events of Special Interest

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

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

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

8. ADVERSE EVENT REPORTING

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

The term “subject” in this section refers to (1) nonpregnant subjects; (2) the maternal subject and her fetus; and after delivery (3) the maternal subject and (4) the infant subject.

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs;

(2) nonserious AEs; and (3) exposure to the investigational product under study during pregnancy (for Stage 1 subjects only), and occupational exposure.

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

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section, Section 8.2.3). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE

Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

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

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

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section, Section 8.1, above.

8.1.4. Time Period for Collecting AE/SAE Information

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

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

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

SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

8.1.4.1. Stage 1

The investigator and site staff will ensure the active elicitation and collection of AEs and SAEs through Visit 3. At Month 6 (Visit 4), the subject will be contacted by telephone to inquire about MAEs and SAEs, including hospitalizations since Visit 3.

Immediate AEs will be reported as detailed in Section 7.8.2.

8.1.4.2. Stages 2 and 3 – Maternal Subjects

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

Immediate AEs will be reported as detailed in Section 7.8.2.

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

8.1.4.3. Stages 2 and 3 – Infant Subjects

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

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

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

Table 8. Time Period for Collecting AE/SAE Information

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

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

8.1.4.4. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form and the Exposure During Pregnancy Supplemental Form (Stage 1 subjects only), if applicable.

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, including miscarriage and missed abortion, intrauterine fetal demise, neonatal death [defined as those deaths that occur within 1 month of birth], or congenital anomaly [defined as structural or functional anomalies (eg, metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life]).[60] These SAEs can occur in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death; the investigator should record this information in the CRF. In addition, infant deaths after 1 month of age should be recorded in the CRF as SAEs.

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

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

The same is applied for those SAEs after the active collection period has ended should they occur to the fetus. In addition, infant deaths that occur after 1 month of age should be reported as SAEs when the investigator believes the death has at least a reasonable possibility of being related to investigational product.

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

8.1.4.5. Recording Nonserious AEs and SAEs on the CRF

All AEs/SAEs occurring in a subject during the active collection period are recorded in the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

The investigator obtains general information on the pregnancy and its outcome for all study subjects. The investigator will follow the pregnancy until completion (or until pregnancy termination). In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, including miscarriage and missed abortion, intrauterine fetal demise, neonatal death [defined as those deaths that occur within 1 month of birth], or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal

death]), the investigator should record this information in the CRF. In addition, infant deaths after 1 month of age should be recorded in the CRF as SAEs.

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);

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

Or that is considered to be:

- An important medical event.

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

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study for subjects enrolled in Stage 1 or the expanded cohorts for Stage 2 and Stage 3. However, should an investigator deem it necessary to assess LFTs because a subject presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

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

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

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

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

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

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

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

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

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

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

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

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

Exposure to the investigational product under study during pregnancy or breastfeeding (applicable only to Stage 1 subjects) and occupational exposure (applicable to subjects in all study stages) are reportable to Pfizer Safety within 24 hours of investigator awareness. Refer to Section 8.1 for further details.

8.4.3.1. Exposure During Pregnancy (Stage 1 Only)

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

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

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

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

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

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

8.4.3.2. Exposure During Breastfeeding

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

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant subject experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

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

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

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

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

8.4.4.1. Medication Errors

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

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Other examples include, but are not limited to:

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

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

9.1. Sample Size Determination

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

Approximately 66 nonpregnant women will be enrolled at Stage 1, 22 subjects per group to receive placebo (saline control) or GBS6 (20 µg CPS/serotype/dose) with or without $AlPO_4$.

Approximately 360 pregnant women will be enrolled at Stage 2, 40 subjects at each GBS6 dose/formulation and a total of 120 subjects in the placebo group. Refer to Table 2 for a detailed description of the number of subjects per group. Approximately 160 pregnant women will be enrolled at Stage 3, 80 subjects at the selected GBS6 dose/formulation and 80 subjects in the placebo group.

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

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

Sample Size (N)	Assumed True Event Rate of an AE					
	1.0%	2.0%	2.5%	3.0%	5.0%	10.0%
14	0.13	0.25	0.30	0.35	0.51	0.77
22	0.20	0.36	0.43	0.49	0.68	0.90
28	0.25	0.43	0.51	0.57	0.76	0.95
40	0.33	0.55	0.64	0.70	0.87	0.99
44	0.36	0.59	0.67	0.74	0.90	0.99
80	0.55	0.80	0.87	0.91	0.98	>0.99
120	0.70	0.91	0.95	0.97	>0.99	>0.99
240	0.91	0.99	>0.99	>0.99	>0.99	>0.99
320	0.96	>0.99	>0.99	>0.99	>0.99	>0.99

Abbreviations: $AlPO_4$ = aluminum phosphate; CPS = capsular polysaccharide.
Note: In Stage 1, 44 nonpregnant women are planned to be vaccinated with GBS6 (20 µg CPS/serotype/dose) with or without $AlPO_4$ (22/formulation). In each sentinel cohort of Stage 2, 28 maternal subjects are planned to be vaccinated with each dose of GBS6 with or without $AlPO_4$ (14/formulation). In Stage 2, a total of 80 maternal subjects are planned to be vaccinated with each dose of GBS6 with or without $AlPO_4$ (40/formulation), and 240 maternal subjects are to be vaccinated with any dose of GBS6 with or without $AlPO_4$ (120/formulation). In the entire study, 320 maternal subjects are to be vaccinated with any dose of GBS6.

9.2. Immunogenicity Analysis

Immunogenicity data will be analyzed separately for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3), and their infant subjects (Stages 2 and 3). In addition, immunogenicity results from maternal subjects (Stages 2 and 3) and their infant subjects (Stages 2 and 3) may be analyzed together as appropriate.

9.2.1. Immunogenicity Analysis Populations

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

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

9.2.1.1. Nonpregnant Women (Stage 1)

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

9.2.1.2. Maternal Subjects (Stages 2 and 3)

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

9.2.1.3. Infant Subjects (Stages 2 and 3)

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

population, the infant subject's mother must be randomized and the infant subject must have at least 1 valid and determinate assay result related to the proposed analysis.

9.2.2. Analysis of Immunogenicity Endpoints

Immunogenicity endpoints are secondary [redacted] in the study as listed in Section 2.2. Descriptive summary statistics will be provided for all immunogenicity endpoints. No formal between-group comparison will be made.

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

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

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

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

[redacted]

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

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

Detailed analyses of all the immunogenicity endpoints [redacted] and graphical displays will be described in the SAP.

9.3. Safety Analysis

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

9.3.1. Safety Population

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

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

9.3.1.1. Nonpregnant Women (Stage 1)

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

9.3.1.2. Maternal Subjects (Stages 2 and 3)

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

9.3.1.3. Infant Subjects (Stages 2 and 3)

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

9.3.2. Analysis of Safety Endpoints

The safety endpoints as listed in Section 2.1 are primary in the study and their analyses are based on the safety population.

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

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

9.4. Analysis Timing

In addition to the planned safety data review while the study is ongoing, 3 interim analyses are planned for this study.

The first interim analysis will be performed when 1-month postvaccination safety data from all subjects enrolled in Stage 1 are available. Stage 2 of the study will be initiated based on results from the first interim analysis as well as those from the 1-month postvaccination safety and immunogenicity data of 3 different dose levels of GBS6 formulated with or without $AlPO_4$ from the prior US FIH Phase 1/2 study (C1091001). Both the IRC and E-DMC will review all 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 6-week postdelivery/birth safety and immunogenicity data from all maternal subjects and their infant subjects in Stage 2 are available. All available safety and immunogenicity data from all study participants will be included in the analysis. The primary objective of the second interim analysis is to select a dose and formulation for Stage 3. These unblinded data will be reviewed by both the IRC and E-DMC. However, the IRC will select the GBS6 final dose and formulation to take into Stage 3 and further development.

The third interim analysis will be performed when 6-week postdelivery/birth safety and immunogenicity data from all maternal subjects and their infant subjects in Stage 3 are available. All available safety and immunogenicity data from all study participants will be included in the analysis. The primary objective of the third interim analysis is to support internal development decisions and potential regulatory agency interactions for the program.

No multiplicity adjustments will be applied for these assessments.

After the completion of the 12-month postdelivery/birth follow-up visit for subjects in Stage 3, a clinical study report (CSR) including all safety and immunogenicity data gathered from all subjects from each of the 3 stages will be issued. Safety and immunogenicity data from maternal subjects who receive the same vaccine dose/formulation or placebo in Stages 2 and 3 will be combined and analyzed together. Safety and immunogenicity data from infant subjects who are born to maternal subjects receiving the same vaccine dose/formulation or placebo in Stages 2 and 3 will be combined and analyzed together.

9.5. Data Monitoring Committee

This study will use both an IRC and an E-DMC.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter, as well as the analysis results with the safety data cutoff at 1 month after vaccination for subjects from Stage 1 as described in Section 9.4 above. The E-DMC will also meet for an ad hoc safety review should enrollment of Stage 2 subjects be halted, to review the IRC recommendation and make a recommendation before enrollment may be restarted, the protocol modified, or enrollment terminated. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

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

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the CSA and applicable privacy laws. The ICDs and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

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

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

or parent(s) if a minor, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

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

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

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

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

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

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

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

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

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

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Appendix 1. Abbreviations

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

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

Abbreviation	Term
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IAP	intrapartum antibiotic prophylaxis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive Web-based response
LFT	liver function test
LMIC	low- and middle-income country
LMP	last menstrual period
LOD	late-onset disease
LSLV	last subject last visit
MAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NaCl	sodium chloride
OPA	opsonophagocytic activity
PCD	primary completion date
PDA	personal digital assistant
PI	principal investigator
PT	prothrombin time
RBC	red blood cell
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document
TBili	total bilirubin
Tdap	tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine

Abbreviation	Term
ULN	upper limit of normal
US	United States
WBC	white blood cell

Document Approval Record

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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	22-May-2018 16:08:30	Final Approval
PPD	22-May-2018 16:46:59	Final Approval

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

Investigational Product Number:	PF-06760805
Investigational Product Name:	Group B Streptococcus 6-Valent Polysaccharide Conjugate Vaccine (GBS6)
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C1091002
Phase:	1/2

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 4	25 November 2020	• Added background information on clinical experience with repeated dosing (Protocol Summary, Section 1.2.3.4). • Added that Stage 1 subjects (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 and provide additional serum to support the development of a universal reference standard assay, which is needed to inform a potential surrogate of protection for the GBS6 vaccine (Protocol Summary, Section 1.2.5). • Updated the objectives and associated analyses to be performed for Stage 1 subjects (nonpregnant women) returning for the booster vaccination (Protocol Summary, Section 1.2.5, Section 2.1, Section 2.2, Section 7.3.2, Section 9.1, Section 9.2.1.1, Section 9.3.1.1). • Updated the study design and study procedures to include details of additional visits and study procedures for Stage 1 subjects (nonpregnant women) returning for the booster vaccination (Protocol Summary, Schedule of Activities, Section 3.1, Section 3.4, Section 3.6, Table 1, Table 2, Section 5, Section 5.8, Sections 6.1.5 to 6.1.10, Section 6.5.1). • Updated the eligibility and temporary delay criteria for Stage 1 subjects (nonpregnant women) returning for the booster vaccination (Section 4.2, Section 4.3, Section 4.8). • Updated the Investigational Products section to include details of the booster vaccination, nonstudy vaccinations, and concomitant medications for Stage 1 subjects (nonpregnant women) returning for the booster vaccination (Section 5, Section 5.2,

Document	Version Date	Summary of Changes and Rationale
		Section 5.4, Sections 5.7 to Section 5.9, Section 5.10.3.1). • Updated the safety monitoring and adverse event (AE) reporting procedures for Stage 1 subjects (nonpregnant women) returning for the booster vaccination (Section 7.8.3, Section 8.1.4, Table 8). • Updated "Clinical Trial (CT) Serious Adverse Event (SAE) Report Form" to "Vaccine SAE Reporting Form" throughout Section 8. • Updated the fourth interim analysis that will be performed when all Stage 3 maternal subjects and their infants have completed the delivery/birth visit and as a protective threshold, once identified, will be based on infant IgG at birth. The interim analysis is being modified to be in line with this strategy (Section 9.4).
Amendment 3	27 May 2020	• The gestational age of vaccination for subjects in Stage 3 has been changed from ≥27 0/7 to ≤35 6/7 weeks' gestation to ≥24 0/7 to ≤35 6/7 weeks' gestation, to enable evaluation of safety and immunogenicity at earlier gestational ages (second trimester) (Protocol Summary, Section 2.1.4, Section 3, and Section 4.4). • The third interim analysis has been updated and will be performed when all Stage 2 maternal subjects and their infants have completed the delivery/birth visit, as a protective threshold, once identified, will be based on infant IgG at birth. The interim analysis is being modified to be in line with this strategy (Protocol Summary, Section 3.2, Section 9.4). • Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks, to enable expanded evaluation of safety and immunogenicity data at the

Document	Version Date	Summary of Changes and Rationale
		selected dose, in the second and third trimester of pregnancy (Section 1.2.5, Section 3.3, Section 3.6, and Section 9.1). • Text was added to Section 6.2 and Section 6.3 and the schedule of activities (Stages 2 and 3) to clarify that study visits can be conducted by telephone in the event of a disease outbreak or pandemic. This will allow for appropriate safety follow-up per protocol requirements. Incorporated the Protocol Administrative Change Letter from March 2020. • The text in Section 6.3.1 and the schedule of activities was updated to allow sites to calculate and record the Ballard score up to 72 hours after delivery. This will allow information to be obtained if unavailable at delivery. Incorporated the Protocol Administrative Change Letter from November 2019. • Added editorial changes in Section 7 and Section 15.1 to improve clarity.
Amendment 2	18 September 2019	• CCI [redacted] • Updated the study procedures section for infant subjects (Section 6.3) to include additional body systems to be evaluated for the physical examination, per regulatory feedback. Incorporated the Protocol Administrative Change Letter from April 2019. • Updated Section 6.3.1 to allow for the collection of delivery visit information from available sources. Incorporated the Protocol

Document	Version Date	Summary of Changes and Rationale
		Administrative Change Letter from August 2019. • Updated the time window for the daily diary collection (Section 7.5.1 and the schedule of activities), since the time window opens in the afternoon (not the evening). Incorporated the Protocol Administrative Change Letter from April 2019. • Updated text in the schedule of activities, Section 8.1.4.2, and Table 8 to clarify that adverse events (AEs) related to study procedures occurring up to 48 hours after the blood draw at Visit 4 should also be reported in the case report form (CRF). Incorporated the Protocol Administrative Change Letter from July 2019.
Amendment 1	04 February 2019	• Added editorial changes throughout the document to improve clarity and to fix typographical errors. • Provided clarification on the timing of internal review committee (IRC) reviews in the Protocol Summary and Section 3.2. [redacted] • Made changes regarding the collection of concomitant medications to the schedule of activities and the Procedures section to ensure consistency with Section 5.10.3. • Made changes to the schedule of activities and the Procedures section for maternal subjects to only measure height at the screening visit, since height is not expected to change significantly during the study.

Document	Version Date	Summary of Changes and Rationale
		• Updated all temperature references to °C (°F) per local practice. • Added a statement confirming the rationale for the collection of date of birth to the Procedures section (Section 6). • Updated Section 6.5.1 to accommodate local requirements for subjects who are lost to follow-up. • Updated Sections 5.8 and 9.4 to include an additional interim analysis that was added for internal planning purposes.
Original protocol	11 May 2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale

Streptococcus agalactiae, also known as group B streptococcus (GBS), is an encapsulated, gram-positive coccus that is associated with lower intestinal and rectovaginal colonization. There are 10 serotypes of GBS (Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX) differentiated by the polysaccharide composition of their capsules. Although all GBS serotypes have been found to cause disease, 6 serotypes (Ia, Ib, II, III, IV, and V) have been found to cause over 85% of disease globally and 98% in South Africa, but there is variability in their global prevalence and virulence. GBS disease is most frequently found in the very young—newborns and infants younger than 3 months of age—and the elderly, especially older adults with comorbid conditions. However, disease due to GBS has been reported in individuals of all ages, and pregnant women may be particularly susceptible to GBS disease as well.

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

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

Vaccination of pregnant women has been used globally in the prevention of neonatal tetanus and more recently for prevention of pertussis in young infants, and to protect women and their infants against influenza. Vaccination with tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women was introduced in the United States and in the United Kingdom in response to a significant upsurge in pertussis cases in all age groups. Maternal immunization against influenza was recommended by the US Advisory

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

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

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

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

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

Primary Objectives

Primary Objective: Stage 1

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

- To describe the safety and tolerability of a booster dose of GBS6 when administered to healthy nonpregnant women.

Primary Objectives: Stage 2

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

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

Primary Objectives: Stage 3

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

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

Primary Endpoints

Primary Endpoints: Stage 1

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

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

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

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

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

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

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

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

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

Primary Safety Endpoints (Infants): Stages 2 and 3

- Proportions of infants with specific birth outcomes.

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

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

Study Design

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of a multivalent GBS vaccine in healthy nonpregnant women and pregnant women aged 18 to 40 years and their infants. A total of approximately 586 subjects (66 nonpregnant women and 520 maternal subjects and their infants) will be enrolled in this study.

Stage 1

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

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

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

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

Stage 1 subjects (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. Subjects will have blood drawn at the prebooster screening visit (Visit 5), prior to the booster vaccination (Visit 6), 1 month after the booster vaccination (Visit 7), 3 months after the booster vaccination (Visit 8), and 6 months after the booster vaccination (Visit 9). E-diaries will be used to collect prompted local reaction and systemic event data for 7 days after the booster vaccination. AEs will be collected through 1 month after vaccination (Visit 7). In addition, MAEs and SAEs will be collected from the booster vaccination visit (Visit 6) through 6 months after the booster vaccination (Visit 9).

Stage 2

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

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

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

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

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

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

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

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

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

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

CCI

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

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

Stage 3

Approximately 160 additional maternal subjects will be enrolled in Stage 3, to receive a single dose/formulation of the selected GBS6 or placebo (saline control) in a 1:1 ratio. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks. There will be no dose escalation, no sentinel cohorts, and no planned stopping rules. The visit schedule, follow-up, and assessments for maternal subjects and their infant subjects will be similar to Stage 2. The additional data from Stage 3 will contribute to the safety database of maternal subjects to support the design the Phase 3 program.

When Stage 3 maternal subjects and their infant subjects have completed the 6-week postdelivery/birth visit, safety and immunogenicity data will be unblinded by group, when available, and analyzed and reviewed by the Pfizer IRC.

Investigational Products

The investigational products are GBS6, composed of CPS of serotypes Ia, Ib, II, III, IV, and V, individually conjugated to CRM_{197} at dose levels of 5, 10, or 20 µg CPS/serotype/dose, formulated with or without $AlPO_4$, or placebo (saline control). At Visit 1, investigational product will be administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm.

Statistical Methods

Statistical analyses will be descriptive in nature. All safety and immunogenicity data will be analyzed separately for nonpregnant women (Stage 1), maternal subjects (Stage 2 and Stage 3), and their infant subjects (Stage 2 and Stage 3). Safety and immunogenicity data from subjects who receive the same vaccine dose/formulation or placebo (saline control) in

Stage 2 and Stage 3 will be combined and analyzed together for maternal subjects and also analyzed together for their infant subjects.

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

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures (Section 6) and Assessments (Section 7) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

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

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

Stage 1 – Schedule of Activities for Nonpregnant Women										
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Description	**Screening**	**Vaccination**	**2-Week Follow-up Visit**	**1-Month Follow-up Visit**	**6-Month Follow-up Telephone Contact**	**Prebooster Screening**	**Booster Vaccination**	**1-Month Booster Vaccination Follow-up Visit**	**3-Month Booster Vaccination Follow-up Visit**	**6-Month Booster Vaccination Follow-up Visit**
Visit Window (Days)[a]	**Day -7 to Day -2 Prior to Day 1**	**Day 1**	**14-17 Days After Visit 1**	**28-42 Days After Visit 1**	**160-200 Days After Visit 1**	**Day -7 to Day -2 Prior to Visit 6**	**~2 Years After Visit 1**	**28-42 Days After Visit 6**	**84-126 Days After Visit 6**	**160-200 Days After Visit 6**
CCI [redacted]										

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

a. Day relative to the start of study vaccination (Day 1).
b. Obtain written informed consent before performing any study specific procedures.
c. Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures, that have been diagnosed since Visit 1.
d. Vital signs include weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
e. Only concomitant medication taken to treat an adverse event will be recorded in the case report form.
f. The contraception check is an opportunity to confirm that contraception was/is used consistently and correctly.
C [redacted]
h. Subjects will record reactogenicity events in an e-diary within a fixed time window each day for 7 days following vaccination. Remind subjects that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary. Ask subjects to contact the investigator or site staff immediately if they are prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required.
i. Designated site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.
C [redacted]

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

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

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

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

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

a. Visits at 2 weeks and 1 month after vaccination will not be performed if delivery occurs before the visits. In that case, hematology and chemistry assessments due at the 2 week visit should be conducted at the delivery visit. Once delivery occurs, the visit windows are calculated based on delivery date.
b. If abnormal laboratory values (as defined in Screening, Section 6.2.1, and in Section 7.5.3) are reported at Visit 0/Visit 2 and the investigator believes the results to be erroneous, the abnormal laboratory parameters may be retested.
c. Vital signs include weight, height (only required at Visit 0), oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
d. Only concomitant medication taken to treat an adverse event will be recorded in the case report form.
e. All blood volumes are approximate.
f. Blood sample may be collected up to 72 hours after delivery.
g. Subjects will provide (in an e-diary) a baseline assessment of prompted systemic events prior to vaccination and subjects will record (in an e-diary) reactogenicity events within a fixed time window each day for 7 days following vaccination. Remind subjects that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary. Ask subjects to contact the investigator or site staff immediately if they are prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required (see Section 6.4).
h. Designated site staff will review e diary data online at frequent intervals for the 7 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.
i. Only adverse events occurring up to 48 hours after each blood draw that are related to study procedures must be recorded in the case report form.

CCI [redacted]

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

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

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

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

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

CCI [redacted]

1. INTRODUCTION

1.1. Indication

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

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

1.2. Background and Rationale

1.2.1. Disease Overview

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

1.2.2. GBS Disease in Infants and Pregnant Women

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

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

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

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

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

In other countries, such as in certain European countries, where interventions are less widely used or a risk-based approach is used, the trend in incidence rates may be unchanged or increasing slightly.[6,26] Neither approach has eliminated GBS disease in infants. Furthermore, many countries around the world do not have the resources to implement IAP.

Even with potential underreporting, the highest rates of GBS disease are found in LMICs,[15] where healthcare access and standards of prenatal care may vary, or the resources for significant preventive interventions are not available.

1.2.3. Rationale for Development of GBS6

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

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

1.2.3.2. Maternal Antibody and Protection Against GBS Disease in Infants

During the third trimester of pregnancy, only IgG antibodies are actively transported across the placenta. This provides a means for protective antibody to be transferred from a mother to her newborn.[34] The efficiency of antibody transfer depends on placental integrity, maternal total IgG, GA at delivery, and IgG subclass (the immunoglobulin G1 [IgG1] subclass is most efficiently transferred).[28] Researchers measured antibody in sera collected at delivery from GBS-colonized mothers whose infants had developed EOD, and in GBS-colonized women whose infants had not developed EOD. There was a correlation between low maternal antibody concentration to serotype III (as measured in an IgG assay) and infant susceptibility to EOD due to serotype III.[35] Since the initial study, additional work was conducted demonstrating the correlation between serotype Ia–specific anti–capsular polysaccharide (CPS) antibody in the mother and protection of the baby against GBS EOD due to serotype Ia, and a directional effect with the serotype V antibody.[36-39] This suggests that anti-CPS antibody protects against GBS disease, a mechanism similar to that exploited against other encapsulated organisms, and the antibody is transported across the placenta. These findings support the biological plausibility that increasing the levels of maternal anti-CPS IgG antibody by vaccination of pregnant women with serotype-specific

polysaccharide conjugate antigens will increase the proportion of women with potentially protective levels of IgG and will result in placental transfer of protective antibody to a large number of infants.

1.2.3.3. Clinical Experience With Polysaccharide Conjugate Vaccines and GBS Polysaccharide Conjugate Vaccine

There is significant experience with the use of polysaccharide conjugate vaccines to prevent disease due to encapsulated bacteria in infants, children, and adults.[40,41] A number of polysaccharide conjugate vaccines have been developed and globally licensed by Pfizer (HibTITER®, Meningitec®, Prevenar®, Prevenar 13®) and other vaccine manufacturers (eg, Menveo, ActHIB, Hiberix). These vaccines have a well-established safety profile and induce high levels of functionally active antibodies that are protective as demonstrated either through efficacy studies or based on established immune correlates of protection.

Investigational GBS polysaccharide conjugate vaccines have been evaluated in clinical trials in pregnant women, including a trivalent (Ia, Ib, and III) GBS CPS–cross-reactive material 197 (CRM_{197}) conjugate vaccine in South Africa.[42,43] These studies demonstrated the acceptable safety profile of GBS polysaccharide conjugate vaccines, as well as the induction of immune responses to the GBS vaccine serotypes in their infants.

1.2.3.4. Clinical Experience With Repeated Doses of Vaccines

There is precedent for repeated doses of vaccines to augment or sustain protection against disease in pregnant women. Several countries recommend the administration of Tdap during every pregnancy, including closely spaced pregnancies. The South African guidelines for maternity care recommend all pregnant women are given a total of 5 properly spaced doses of tetanus toxoid immunization to provide life-long protection against tetanus. The guidelines recommend 3 tetanus toxoid immunization doses during the first pregnancy and 2 tetanus toxoid immunization booster doses for the next 2 subsequent pregnancies, 1 in each pregnancy, at least 1 year apart.[44] Published data report that vaccination with Tdap during pregnancy is not associated with an increased risk of adverse birth outcomes[45] and suggest that repetitive dosing in a short time span in serial pregnancies does not unfavorably affect pregnancy. In 1 study, no adverse pregnancy, delivery, or neonatal outcomes were observed in association with antepartum Tdap vaccination in women who received more than 1 antepartum Tdap vaccinations spaced in a 5-year time frame.[46]

Data are available regarding the boosting of IgG responses from Phase 1 and 2 clinical trials of other GBS candidate vaccines. In 1 study, a second dose of an investigational trivalent GBS vaccine, administered 4 to 6 years after the first dose, elicited a robust immune response for each vaccine serotype in nonpregnant women, including in those with undetectable pre– first dose anti-GBS antibody levels. The authors suggest a sufficiently spaced second vaccine dose may be beneficial for women with very low preexisting antibody concentrations.[47] In another study investigating a different GBS candidate vaccine, a second dose of GBS type III CPS-tetanus toxoid conjugate vaccine (GBS III-TT) given 21 months after the first dose restored type III CPS-specific IgG antibody levels to those obtained after the primary vaccination. The ability of a second dose to augment the immune response was

apparent only in the subset of healthy adults who had very low concentrations (<0.05 µg/mL) of CPS-specific IgG prior to vaccination. In this group, the second dose resulted in specific IgG GMCs that were 3-fold higher than that obtained after a single dose.[48] These data suggest that repeat vaccination is safe and may offer immunologic benefit.

1.2.4. Group B Streptococcus 6-Valent Polysaccharide Conjugate Vaccine

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

The GBS6 candidates are composed of polysaccharides of the 6 most prevalent serotypes causing >95% of GBS disease in infants, individually conjugated to the CRM_{197} carrier protein. They contain 5, 10, or 20 µg CPS/serotype/dose, and are formulated with or without aluminum phosphate ($AlPO_4$). Refer to Table 3 for further details. The candidates have been developed based on Pfizer historical experience with licensed and investigational polysaccharide conjugate vaccines, published/public data with other investigational GBS polysaccharide conjugate vaccines, and data from the preclinical models of GBS6.[41,49-57]

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

The formulations with $AlPO_4$ may offer particular advantages in immune response based on their potential to drive an IgG1 antibody response, which is the antibody subclass preferentially transported across the placenta.[60,61] Therefore, GBS6 formulated with $AlPO_4$ is being assessed in early clinical development to determine the optimal formulation that induces maximally protective antibody levels in humans.

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

1.2.5. Study Rationale

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

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

Stage 2 will commence following a review of the 1-month postvaccination safety data from the Phase 1/2 LMIC Stage 1 cohort and 1-month postvaccination safety and immunogenicity data from the Phase 1/2 FIH study (C1091001). If the safety and immunogenicity profile is deemed acceptable, the safety, tolerability, and immunogenicity of 3 ascending dose levels (5, 10, or 20 µg CPS/serotype/dose) of GBS6 formulated with or without $AlPO_4$ will be assessed when administered as a single dose to healthy pregnant women aged 18 to 40 years during their 27 to 36 weeks of pregnancy. Of note, all 3 dose levels (5, 10, or 20 µg CPS/serotype/dose) may not be evaluated during Stage 2 should any dose/formulation level be deemed unacceptable after review of immunogenicity data from the Phase 1/2 FIH study (C1091001) and the safety data from Stage 1 of the C1091002 study.

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

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

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

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

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives and Endpoints

2.1.1. Primary Objective: Stage 1

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

- To describe the safety and tolerability of a booster dose of GBS6 when administered to healthy nonpregnant women.

2.1.2. Primary Endpoints: Stage 1

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

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

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

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

2.1.3. Primary Objectives: Stage 2

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

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

2.1.4. Primary Objectives: Stage 3

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

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

2.1.5. Primary Safety Endpoints (Maternal Subjects): Stages 2 and 3

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

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

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

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

2.1.6. Primary Safety Endpoints (Infant Subjects): Stages 2 and 3

- Proportions of infant subjects with specific birth outcomes.

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

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

2.2. Secondary Objectives and Endpoints

2.2.1. 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.

2.2.2. Secondary Objective: Stage 2

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

2.2.3. Secondary Objective: Stage 3

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

2.2.4. Secondary Objectives: Stages 2 and 3

- To describe GBS6 antibody levels in infant subjects delivered to maternal subjects vaccinated with GBS6.

- To assess placental transfer of antibody from maternal subjects vaccinated with GBS6 to their infant subjects.

2.2.5. Secondary Endpoints: Stage 1

- GBS serotype-specific IgG geometric mean concentrations (GMCs) 1 month after vaccination in nonpregnant women.

- GBS serotype-specific OPA geometric mean titers (GMTs) measured 1 month after vaccination in nonpregnant women.

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

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

2.2.6. Secondary Endpoints (Maternal Subjects): Stages 2 and 3

- GBS serotype-specific IgG GMCs measured at 2 weeks and 1 month after vaccination and at delivery in maternal subjects.

- GBS serotype-specific OPA GMTs measured at 2 weeks and 1 month after vaccination and at delivery in maternal subjects.

2.2.7. Secondary Endpoints (Infant Subjects): Stages 2 and 3

- GBS serotype-specific IgG GMCs in infant subjects measured at birth.

- GBS serotype-specific OPA GMTs in infant subjects measured at birth.

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3. STUDY DESIGN

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

3.1. Stage 1

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

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

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

Stage 1 subjects (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. Subjects will have blood drawn at the prebooster screening visit, prior to the booster vaccination (Visit 6), 1 month after the booster vaccination (Visit 7), 3 months after the booster vaccination (Visit 8), and 6 months after the booster vaccination (Visit 9). E-diaries will be used to collect prompted local reaction and systemic event data for 7 days after the booster vaccination. AEs will be collected through 1 month after vaccination (Visit 7). In addition, MAEs and SAEs will be collected from the booster vaccination visit (Visit 6) through 6 months after the booster vaccination (Visit 9).

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

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

- enrollment in the sentinel cohort for the next higher dose level (see Table 2).

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

This study will use stopping rules for the sentinel cohort, and 1 stopping rule (serious, unexpected AE considered possibly related to vaccine) will also apply to the expanded-cohort enrollment phase. Stopping rules (and the decision to terminate or restart at a given dose level) may be applied independently for each formulation at the discretion of the Pfizer IRC in conjunction with the E-DMC recommendations (therefore, it is possible that

after a stopping rule is met at a given dose level, one formulation [with or without $AlPO_4$] may proceed while the other may not).

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

When all Stage 2 sentinel-cohort maternal subjects and their infant subjects have completed the delivery/birth visit, safety and immunogenicity data will be unblinded and reviewed, when available, by the IRC for Pfizer informational and planning purposes. For details of sponsor blinding, refer to Section 5.8.

When all Stage 2 maternal subjects and their infant subjects have completed the delivery/birth visit, safety and immunogenicity data will be unblinded by group, when available, analyzed, and reviewed by the Pfizer IRC. The final GBS6 dose and formulation to take into Stage 3 and further development will be selected after this review. For details of sponsor blinding, refer to Section 5.8.

3.3. Stage 3

Approximately 160 additional maternal subjects will be enrolled into Stage 3, to receive a single dose/formulation of the selected GBS6 or placebo (saline control) in a 1:1 ratio. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks. There will be no dose escalation, no sentinel cohorts, and no planned stopping rules. The visit schedule, follow-up, and assessments for maternal subjects and their infant subjects will be similar to those in Stage 2. The additional data from Stage 3 will contribute to the safety database of maternal subjects to support the design of the Phase 3 program.

When Stage 3 maternal subjects and their infant subjects have completed the 6-week postdelivery/birth visit, safety and immunogenicity data will be unblinded by group, when available, and analyzed and reviewed by the Pfizer IRC.

Table 1. Enrollment and Dose Escalation Design

<table>
<tr><th colspan="2">Dose Escalation</th><th>Stage 1
Nonpregnant
Women</th><th>Stage 1 Safety Data Review by Pfizer IRC and E-DMC[a]</th><th colspan="6">Stage 2
Maternal Subjects</th><th>Stage 2 Safety and Immunogenicity Review/Dose Selection</th><th>Stage
3 Maternal
Subjects</th></tr>
<tr><td rowspan="3">Lowest Dose</td><td rowspan="3">- GBS6 lowest dose with $AlPO_4$
- GBS6 lowest dose without $AlPO_4$
- Placebo (saline control)</td><td rowspan="3"></td><td rowspan="3"></td><td>Enroll sentinel cohort (n=42)</td><td>14-Day safety review by IRC</td><td colspan="2">Complete enrollment of expanded[b] cohort(n=78)</td><td colspan="2" rowspan="3"></td><td rowspan="3"></td><td rowspan="3">Enroll and vaccinate (n=160, GBS6 selected[c] or placebo (saline)</td></tr>
<tr><td colspan="2" rowspan="2"></td><td>Enroll sentinel cohort[b] (n=42)</td><td>14-Day safety review by IRC</td></tr>
<tr><td colspan="2">Complete enrollment of expanded cohort[b] (n=78)</td></tr>
<tr><td rowspan="3">Middle Dose</td><td rowspan="3">- GBS6 middle dose with $AlPO_4$
- GBS6 middle dose without $AlPO_4$
- Placebo (saline control)</td><td rowspan="3"></td><td colspan="3" rowspan="3"></td><td colspan="2" rowspan="2"></td><td colspan="2" rowspan="2">Complete enrollment of expanded cohort[b] (n=78)</td><td rowspan="3"></td></tr>
<tr><td colspan="2">Enroll sentinel cohort[b] (n=42)</td><td>14-Day safety review by IRC</td></tr>
<tr><td colspan="4" rowspan="2"></td><td colspan="2" rowspan="2"></td></tr>
<tr><td rowspan="3">Highest Dose</td><td rowspan="3">- GBS6 highest dose with $AlPO_4$
- GBS6 highest dose without $AlPO_4$
- Placebo (saline control)</td><td rowspan="3">Enroll and vaccinate[d] (n=66)</td><td rowspan="3"></td><td colspan="4" rowspan="3"></td><td rowspan="3">Enroll sentinel cohort[b] (n=42)</td><td rowspan="3">14-Day safety review by IRC</td><td rowspan="3">Complete enrollment of expanded cohort (n=78)</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2"></td></tr>
</table>

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

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

3.4. Duration of Subject Participation

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

3.5. Duration of Study

The study duration will be approximately 48 months.

3.6. Number of Subjects

Refer to Table 2 below for a detailed description of the number of subjects per stage and dose/formulation group. Subjects who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal. A total of approximately 586 subjects (66 nonpregnant women and 520 maternal subjects and their infant subjects) will be enrolled in this study by central randomization.

3.6.1. Stage 1

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

3.6.2. Stage 2

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

3.6.3. Stage 3

Approximately 160 maternal subjects will be enrolled into Stage 3, 80 at the selected GBS6 dose/formulation and 80 in the placebo group. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks.

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

Stage 1 Dose/Formulation Group[a]		Total (1:1:1)		
Highest Dose[b]	GBS6 (20 µg CPS/serotype/dose) with $AlPO_4$	22		
	GBS6 (20 µg CPS/serotype/dose) without $AlPO_4$	22		
	Placebo (saline control)	22		
Stage 2 Dose/Formulation Groups		**Sentinel (1:1:1)**	**Expanded (1:1:1)**	**Total**
Lowest Dose	GBS6 lowest dose with $AlPO_4$	14	26	40
	GBS6 lowest dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[c]
Middle Dose	GBS6 middle dose with $AlPO_4$	14	26	40
	GBS6 middle dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[c]
Highest Dose	GBS6 highest dose with $AlPO_4$	14	26	40
	GBS6 highest dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[c]
Stage 3 Dose/Formulation Group		**Total (1:1)**		
Selected Dose	Selected GBS6 dose/formulation	80		
	Placebo (saline control)	80		

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

a. Stage 1 subjects (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 (20 µg CPS/serotype/dose with $AlPO_4$) approximately 2 years after the primary dose of investigational product.
b. One hundred four healthy adults (males and females) aged 18 to 49 years 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 subjects receiving placebo (saline control) in total in Stage 2.

4. SUBJECT ELIGIBILITY CRITERIA

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

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria – Stage 1

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

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

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

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

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

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

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

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

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

   c. Have medically confirmed ovarian failure.

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

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

4.2. Inclusion Criteria – Stage 1 Booster Vaccination

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

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

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

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

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

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

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

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

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

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

   c. Have medically confirmed ovarian failure.

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

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

4.3. Exclusion Criteria – Stage 1

Subjects with any of the following characteristics/conditions will not be included in the study:

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

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

3. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

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

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

6. Immunocompromised subjects with known or suspected immunodeficiency.

7. Subjects who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt through the 1-month postvaccination blood draw. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, subjects should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 30 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

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

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

10. Current alcohol abuse or illicit drug use.

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

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

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

14. Female subjects who are breastfeeding.

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

4.4. Inclusion Criteria – Stages 2 and 3 – Maternal Subjects

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

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

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

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

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

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

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

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

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

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

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

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

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

      - If there is a discrepancy of >21 days between the LMP-determined GA and the third-trimester ultrasound OR if the LMP is uncertain/unknown, then the GA should be determined using the third-trimester ultrasound.

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

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

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

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

4.5. Exclusion Criteria – Stages 2 and 3 – Maternal Subjects

Subjects with any of the following characteristics/conditions will not be included in the study:

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

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

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

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

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

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

7. Current alcohol abuse or illicit drug use.

8. Body mass index (BMI) of $\geq$40 kg/m^2 at the time of the screening visit.

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

10. Subjects with known or suspected immunodeficiency.

11. Subjects who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt through the postvaccination blood draw. If systemic corticosteroids have been

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

12. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

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

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

15. Vaccination with diphtheria- or CRM_{197}-containing vaccine, from 6 months before investigational product administration.

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

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

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

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

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

4.6. Inclusion Criteria – Infant Subjects – Stages 2 and 3

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

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

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

4.7. Exclusion Criteria – Infant Subjects – Stages 2 and 3

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

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

The following conditions are temporary or self-limiting and a subject may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met. The prevaccination immunogenicity blood draw and vaccination should take place on the same day (Visit 1 and Visit 6 [Stage 1 only]).

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

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

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

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

4.9. Lifestyle Requirements

4.9.1. Contraception (Stage 1 Subjects Only)

All female subjects who are of childbearing potential and are sexually active with 1 or more members of the opposite sex must agree to use a highly effective method of contraception consistently and correctly for at least 3 months after administration of investigational product. The investigator or his or her designee, in consultation with the subject, will

confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the schedule of activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

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

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

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

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

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

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

4.10. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the

established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. INVESTIGATIONAL PRODUCTS

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

For this study, the investigational product(s) are GBS6 (containing 5, 10, or 20 µg CPS/serotype/dose, each formulated with or without $AlPO_4$) and placebo (saline control). Subjects will receive 1 dose of either GBS6, with or without $AlPO_4$, or placebo (saline control) at Visit 1 administered intramuscularly by [redacted], preferably of the nondominant arm. The dose level/formulation received by each subject will be based on which stage of the study the subject will be enrolled in (see Table 1).

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

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

5.1. Investigational Product Supplies

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

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

5.1.1. Dosage Form(s) and Packaging

GBS6 is composed of serotypes Ia, Ib, II, III, IV, and V CPS [redacted] There are 3 dose levels (5, 10, or 20 µg CPS/serotype/[redacted]), each formulated either with $AlPO_4$, [redacted], or without $AlPO_4$. See Table 3 for further details.

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

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

5.1.2. Preparation and Dispensing

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

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

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

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

5.2. Allocation to Investigational Product

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

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

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

5.3. Subject Compliance

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

5.4. Administration

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

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

Investigational product administration details will be recorded on the case report form (CRF).

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

GBS6 or placebo (saline control) should be administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm.

5.5. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. Investigational products should be stored in their original containers and in accordance with the labels.

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

The unblinded dispenser/administrator will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

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

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

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer. Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be

considered a protocol deviation. CCI [redacted]

5.6. Investigational Product Accountability

The unblinded dispenser/administrator at the investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Blinding of the Site Personnel

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

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

5.8. Blinding of the Sponsor

In each stage of the study, sponsor study team members will remain blinded to vaccine assignment of all subjects enrolled in that stage, following the principles outlined in ICH E9 guideline on Statistical Principles for Clinical Trials, Section 2.3.1,[62] until the planned interim analyses in that stage. Four unblinded interim analyses are planned in the study (refer to Section 9.4). For the second interim analysis, the study team will only be unblinded for the sentinel-cohort data and will remain blinded for all expanded cohorts. In an event that unblinded results need to be submitted for regulatory communications prior to study team unblinding, efforts will be made to ensure study team members involved in subject assessments are blinded.

Certain sponsor personnel not directly involved in the conduct of the study will review unblinded data as defined in an IRC charter per Pfizer standard operating procedures (SOPs). Unblinded sponsor personnel who are not part of the study team will be assigned to assess

whether a stopping rule is triggered for ongoing safety review as well as to work with an independent statistical team center for IRC review activities. Laboratory personnel performing the immunologic assays will remain blinded to vaccine assigned/received throughout the study.

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

5.9. Breaking the Blind

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

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

5.10. Concomitant Treatment(s)

5.10.1. Prohibited Nonstudy Vaccines and Medications During the Study

5.10.1.1. Stage 1

- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study.
- Nonstudy diphtheria- and CRM_{197}-containing vaccines, blood/plasma products or immunoglobulins, and immunosuppressive therapy are prohibited during the course of the study.
- Other nonstudy vaccines may not be given concomitantly with the investigational product or within 14 days after investigational product administration (except during an outbreak or pandemic situation).

5.10.1.2. Stages 2 and 3 – Maternal Subjects

- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study.
- Nonstudy diphtheria- and CRM_{197}-containing vaccines, blood/plasma products or immunoglobulins (except anti-D immunoglobulin, eg, RhoGAM, which can be given at any time), and immunosuppressive therapy are prohibited during the course of the study.
- Other nonstudy vaccines may not be given concomitantly with the investigational product or within 14 days after investigational product administration (except during an outbreak or pandemic situation).

5.10.2. Permitted Nonstudy Vaccines and Medications During the Study

5.10.2.1. Stage 1

- Licensed influenza vaccine may be given during the study starting 15 days after investigational product administration. If medically necessary (eg, pandemic), influenza vaccine may be given at any time.

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

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

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

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

5.10.2.2. Stages 2 and 3 – Maternal Subjects

- Licensed influenza vaccine, and tetanus vaccines may be given during the study starting 15 days after investigational product administration as per local recommendation for immunization in pregnant women. If medically necessary (eg, pandemic), influenza vaccine may be given at any time.

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

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

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

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

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

5.10.2.3. Stages 2 and 3 – Infant Subjects

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

5.10.3. Recording Nonstudy Vaccinations and Concomitant Medications

5.10.3.1. Stage 1

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

Any medications taken from the signing of ICD through Visit 3 (1-month follow-up visit) will be recorded in the CRF. Additionally, any medication taken to treat AEs from the signing of the ICD through Visit 4 will be recorded in the CRF. For subjects receiving the booster vaccination, medications taken from the signing of ICD (Visit 5) through Visit 7 (1-month booster vaccination follow-up) will be collected and recorded in the CRF. Additionally, any medication taken to treat AEs from the signing of the ICD (Visit 5) through Visit 9 will be recorded in the CRF.

5.10.3.2. Stages 2 and 3 – Maternal Subjects

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

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

5.10.3.3. Stages 2 and 3 – Infant Subjects

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

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

6. STUDY PROCEDURES

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

6.1. Stage 1 Study Procedures – Nonpregnant Women

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

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

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

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

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Assign a single subject identifier using the IRT system.
- Obtain and record the subject demography (including date of birth, sex, race, and ethnicity). The complete date of birth (dd-mmm-yyyy) will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record any medical history of clinical significance.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 4).

- Obtain a blood sample (approximately 5 mL) for HIV, HBV, and HCV testing. Subjects testing positive for HIV, acute or chronic HBV, or HCV will not be eligible for randomization.
- Complete the source documents.
- Record nonstudy vaccinations and medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.1.2. Visit 1 – Vaccination (Day 1)

- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in Section 6.5, and meets none of the temporary delay criteria as described in Section 4.8.
- Review screening laboratory results.
- Prior to vaccination, measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Prior to vaccination, perform a urine pregnancy test for female subjects of childbearing potential.
- Prior to vaccination, collect a blood sample of approximately 15 mL for immunogenicity assessments.
- [redacted]
- Verify understanding of and compliance with protocol requirements for contraception.
- A blinded site staff member will use the IRT system to obtain the subject's randomization number. An unblinded site staff member will use the IRT to assign investigational product container number, and will prepare the investigational product and deliver it to the investigational product administrator. Please refer to the IP manual for further instruction on this process.
- The unblinded administrator administers a single 0.5-mL injection of investigational product into the deltoid muscle, preferably of the nondominant arm.

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

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

- Issue the subject an e-diary and provide instructions on its completion. Ask the subject to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

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

- Remind subjects that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary.

- Ask the subject to contact the site staff or investigator if a medically attended event (eg, emergency room) or hospitalization occurs.

- Complete the subject's source documents.

- Record nonstudy vaccinations and concomitant medications as described in Section 5.10.3.

- Record AEs as described in Section 7.8 and Section 8.

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

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

6.1.3. Visit 2 – 2-Week Follow-up Visit (14-17 Days After Visit 1)

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.

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

- Collect a blood sample of approximately 15 mL for immunogenicity assessments.

[redacted]

- Review the subject's e-diary data and collect the e-diary. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Complete the subject's source documents.
- Record nonstudy vaccinations and medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.1.4. Visit 3 – 1-Month Follow-up Visit (28-42 Days After Visit 1)

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.

[redacted]

- Complete the subject's source documents.
- Record nonstudy vaccinations and concomitant medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

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

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

- Complete the subject's source documents.
- Record concomitant medications as described in Section 5.10.3. Only concomitant medication taken to treat an AE will be recorded in the CRF.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

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

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

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures, that have been diagnosed since Visit 1.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 4).
- Obtain a blood sample (approximately 5 mL) for HIV, HBV, and HCV testing. Subjects testing positive for HIV, acute or chronic HBV, or HCV will be withdrawn from further participation in the study.
- Collect an additional blood sample of approximately 25 mL.
- Complete the source documents.

- Record nonstudy vaccinations and concomitant medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject is eligible for the booster vaccination and meets none of the temporary delay criteria as described in Section 4.8.
- Review screening laboratory results.
- Prior to vaccination, measure oral temperature.
- Prior to vaccination, perform a urine pregnancy test for female subjects of childbearing potential.
- Prior to vaccination, collect a blood sample of approximately 140 mL.
- Verify understanding of and compliance with protocol requirements for contraception.
- Use the IRT to assign investigational product container number and prepare and administer a single 0.5-mL injection of investigational product into the deltoid muscle, preferably of the nondominant arm. Please refer to the IP manual for further instruction on this process.
- Site staff must observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions in the subject's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions and a digital thermometer for recording daily temperatures, and provide instructions on their use.
- Issue the subject an e-diary and provide instructions on its completion. Ask the subject to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the subject to contact the site staff or investigator immediately if prompted by the e-diary from Day 1 to Day 7 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring ≥21 measuring device units [≥10.5 cm]).
- Remind subjects that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary.

- Ask the subject to contact the site staff or investigator if a medically attended event (eg, emergency room) or hospitalization occurs.
- Complete the subject's source documents.
- Record nonstudy vaccinations and concomitant medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.
- Designated site staff will review e-diary data online at frequent intervals for the 7 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 140 mL.
- Review the subject's e-diary data and collect the e-diary. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Complete the subject's source documents.
- Record nonstudy vaccinations and concomitant medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Verify understanding of and compliance with protocol requirements for contraception.

- Collect a blood sample of approximately 140 mL.
- Complete the subject's source documents.
- Record concomitant medications as described in Section 5.10.3. Only concomitant medication taken to treat an AE will be recorded in the CRF.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 140 mL.
- Complete the subject's source documents.
- Record concomitant medications as described in Section 5.10.3. Only concomitant medications taken to treat an AE will be recorded in the CRF.
- Record AEs as described in Section 7.8 and Section 8
- The investigator or an authorized designee completes the CRF.

6.2. Stage 2 and 3 Study Procedures – Maternal Subjects

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

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

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

For Stage 2 sentinel-cohort subjects only: In the 14-day screening period, retesting of the screening blood/chemistry laboratory parameters will be allowed at the discretion of the investigator if the investigator believes the results to be erroneous. In this circumstance, subjects will return for a second screening visit within the 14-day screening period to reevaluate the screening laboratory parameters (see Section 6.2.2).

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

The following procedures will be performed:

- Obtain written informed consent before performing any study-specific procedures.
- Assign a single subject identifier using the IRT system.
- Obtain and record the subject demography (including date of birth, sex, race, and ethnicity). The complete date of birth (dd-mmm-yyyy) will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record current alcohol and tobacco usage.
- Obtain and record any medical and obstetric history of clinical significance including history from prior and current pregnancy(ies). Refer to the SRM for further details.
- Record the last normal menstrual period (LMP) and estimated date of delivery (EDD).
- Measure vital signs, including weight, height, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Perform obstetric examination including but not limited to scars from previous deliveries, fundal height, fetal heart tones, and fetal movement.
- Perform obstetric ultrasound and record findings.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 4).
- Obtain blood sample (approximately 10 mL) for HBV, HCV, HIV, and syphilis testing. Subjects testing positive for HIV, acute or chronic HBV, HCV, or syphilis will not be eligible for randomization.
- Stage 2 sentinel cohort only: Obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments. The following parameters will be assessed:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelets.
- Blood chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.

- Obtain urine sample for glucose and protein testing (urine dipstick).
- Complete the source documents.
- Record nonstudy vaccinations and medications (including antibiotic medications) as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

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

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met (see Section 4).
- Obtain a blood sample (approximately 10 mL) for analysis of hematology and blood chemistry assessments (see Section 7.5.3). Retest only abnormal laboratory parameters from Visit 0.
- Complete the source documents.
- Record nonstudy vaccinations and medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

6.2.3. Visit 1 – Vaccination (Day 1) Visit

- Review laboratory results.
- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in Section 6.5, and meets none of the temporary delay criteria as described in Section 4.8.
- Prior to vaccination, measure vital signs, including weight, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the subject's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Obtain urine sample for glucose and protein testing (urine dipstick).
- Issue the subject an e-diary and provide instructions on its completion. Ensure that the subject records a baseline assessment of prompted systemic events in the e-diary prior to vaccination.
- Prior to vaccination, collect a blood sample of approximately 15 mL for immunogenicity assessments.

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- A blinded site staff member will use the IRT system to obtain the subject's randomization number. An unblinded site staff member will use the IRT to assign investigational product container number, and will prepare the investigational product and deliver it to the investigational product administrator. Please refer to the IP manual for further instruction on this process.
- The unblinded administrator administers a single 0.5-mL injection of investigational product into the deltoid muscle, preferably of the nondominant arm.

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

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

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

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

- Remind subjects that study staff may contact them to obtain additional information on Grade 3 events entered into the e-diary.

- Ask the subject to contact the site staff or investigator if a medically attended event (eg, emergency room) or hospitalization occurs.

- Complete the subject's source documents.

- Record nonstudy vaccinations and concomitant medications (including antibiotic medications) as described in Section 5.10.3.

- Record AEs as described in Section 7.8 and Section 8.

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

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

6.2.4. Visit 2 – 2-Week Follow-up Visit (14-17 Days After Visit 1)

If delivery occurs before this visit, this visit will not be conducted; however, the hematology and chemistry assessments planned to be collected at this visit should be conducted at the delivery visit, if possible. For the other procedures to be conducted at delivery, see Section 6.2.6.

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.

- Measure vital signs, including weight, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the subject's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- **Stage 2 sentinel cohort only:** Obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments. The following parameters will be assessed:
    - Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, and platelets.
    - Blood chemistries: ALT, AST, alkaline phosphatase, total bilirubin, BUN, and creatinine.
    - Retesting of abnormal laboratory parameters will be allowed at the discretion of the investigator if the investigator believes the results to be erroneous.
- Review the subject's e-diary data and collect the e-diary. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Complete the subject's source documents.
- Record nonstudy vaccinations and concomitant medications (including antibiotic medications) as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.2.5. Visit 3 – 1-Month Follow-up Visit (28-42 Days After Visit 1)

If delivery occurs before this visit, please conduct the delivery visit instead. For procedures to be conducted at delivery, see Section 6.2.6.

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.

- Measure vital signs, including weight, oral temperature, sitting blood pressure and pulse rate, and respiratory rate.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the subject's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Perform obstetric examination including but not limited to fundal height, fetal heart tones, and fetal movement.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.

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- Complete the subject's source documents.
- Record nonstudy vaccinations and medications (including antibiotic medications) as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.2.6. Visit 4 – Delivery

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Record nonstudy vaccinations, any medication taken to treat AEs, and antibiotic medications as described in Section 5.10.3.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments. The blood sample may be collected up to 72 hours after delivery. Refer to the SRM for blood sample collection guidelines.

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- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.

- Record pregnancy outcome information.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5. This telephone contact should be performed by the investigator or a medically qualified member of the study site staff.
- Complete the subject's source documents.
- Record any medication taken to treat AEs and antibiotic medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.2.8. Visit 6 – 6-Week Postdelivery Follow-up (35-49 Days After Delivery)

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Perform a targeted physical examination, evaluating any clinically significant abnormalities based on history and the subject's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- [redacted]
- Complete the subject's source documents.
- Record any medication taken to treat AEs and antibiotic medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Complete the subject's source documents.
- Record any medication taken to treat AEs and antibiotic medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Complete the subject's source documents.
- Record any medication taken to treat AEs and antibiotic medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Collect a blood sample of approximately 15 mL for immunogenicity assessments.
- Complete the subject's source documents.
- Record any medication taken to treat AEs and antibiotic medications as described in Section 5.10.3.
- Record AEs as described in Section 7.8 and Section 8.
- The investigator or an authorized designee completes the CRF.

6.3. Stage 2 and 3 Study Procedures – Infant Subjects

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

6.3.1. Visit 1 – Delivery

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Assign a single subject identifier.
- Record demography (including date of birth, sex, race, and ethnicity) and available birth information, including but not limited to infant subject vital status (live, stillbirth, neonatal death), appearance, pulse, grimace, activity, and respiration (Apgar) score, birth length, birth weight, head circumference, and Ballard score. If the Ballard score is unavailable, it may be calculated and recorded up to 72 hours after delivery. The complete date of birth (dd-mmm-yyyy) will be collected to critically evaluate the antibody levels and safety profile by age.
- Record available vital signs, including axillary temperature, pulse rate, and respiratory rate.
- Record physical examination evaluating any clinically significant abnormalities within the following available body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Collect a cord blood sample of approximately 10 mL for immunogenicity assessments. If cord blood is unavailable, a blood sample of approximately 2.5 mL may be collected in the infant subjects up to 72 hours after delivery. Refer to the SRM for blood sample collection guidelines.
- Blood spot card collection will be performed using the cord blood sample, or blood draw (up to 72 hours after delivery) if cord blood is unavailable. Refer to the SRM for further details.

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- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines and concomitant medications (including antibiotic medications) as described in Section 5.10.3.

- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Collect and record breastfeeding information.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines and concomitant medications (including antibiotic medications) as described in Section 5.10.3.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Collect a blood sample of approximately 5 mL for immunogenicity assessments. Refer to the SRM for blood sample collection guidelines.
- [redacted]
- Collect and record breastfeeding information.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines and concomitant medications (including antibiotic medications) as described in Section 5.10.3.

- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.
- Collect a blood sample of approximately 5 mL for immunogenicity assessments. Refer to the SRM for blood sample collection guidelines.

[redacted]

- Collect and record breastfeeding information.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines, any medication to taken treat AEs, and antibiotic medications as described in Section 5.10.3.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.

- Collect a blood sample of approximately 5 mL for assessment of antibody responses to routine pediatric vaccines. Refer to the SRM for blood sample collection guidelines.
- Collect and record breastfeeding information.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines, any medication taken to treat AEs, and antibiotic medications as described in Section 5.10.3.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Collect and record breastfeeding information.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines, any medication taken to treat AEs, and antibiotic medications as described in Section 5.10.3.
- The investigator or an authorized designee completes the CRF.

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

- Ensure that the subject continues to be eligible for the study and meets none of the subject withdrawal criteria as described in Section 6.5.
- Measure vital signs, including weight, height, head circumference, axillary temperature, pulse rate, and respiratory rate.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; genitourinary; back; neurological; and lymph nodes. Abnormal results must be recorded on source documents and the physical examination page of the CRF.

- Collect a blood sample of approximately 5 mL for assessment of antibody responses to routine pediatric vaccines. Refer to the SRM for blood sample collection guidelines.
- Collect and record breastfeeding information.
- Complete the subject's source documents.
- Record AEs as described in Section 7.8 and Section 8.
- Record nonstudy vaccines, any medication taken to treat AEs, and antibiotic medications as described in Section 5.10.3.
- The investigator or an authorized designee completes the CRF.

6.4. Unscheduled Visit (Stages 1, 2, and 3 – Maternal Subjects)

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

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

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

If the subject is unable to attend the unscheduled visit, any ongoing reactions must be assessed at the next scheduled visit.

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

- Measure oral temperature.
- Measure minimum and maximum diameters of redness (if present).

- Measure minimum and maximum diameters of swelling (if present).
- Assess any injection site pain that is present in accordance with the grading scale provided in Section 7.5.2.
- Assess for lymphadenopathy associated with any present local reaction.
- Assess any systemic events (nausea/vomiting, diarrhea, headache, fatigue, muscle pain, or joint pain) that are present in accordance with the grading scale provided in Section 7.5.2.

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

Subjects will also be instructed to contact site staff if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for headache, fatigue, muscle pain, joint pain, etc) within 7 days after vaccination. Study staff may contact the subject to obtain additional information on Grade 3 events entered into the e-diary. Lastly, subjects will be instructed to contact the site to report any significant illness, medical event, or hospitalization that occurs during the study period. The site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

6.5. Subject Withdrawal

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

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

6.5.1. Withdrawal of Consent

After investigational product administration at Visit 1 and Visit 6 (Stage 1 only), subjects (nonpregnant women in Stage 1; maternal subjects, and parents of infant subjects born to maternal subjects in Stages 2 and 3) who request to discontinue further study procedures (eg, blood draws) at upcoming visits will be asked to remain in the study for protocol-specified safety follow-up procedures. The only exception to this is when a subject or parent specifically withdraws consent for any further contact. It is permissible that Visit 4

and Visit 9 (Stage 1 subjects), Visit 9 (Stage 2 and 3 maternal subjects), and Visit 7 (Stage 2 and 3 infant subjects) be conducted via telephone contact for subjects who are staying in the study for protocol-specified safety follow-up procedures only. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further study procedures (eg, blood draws) and/or postvaccination study safety follow-up, and entered on the appropriate CRF page.

Lost to follow-up:

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

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

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

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

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

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

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

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be

collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

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

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

7.1. Pregnancy Testing (Applicable to Stage 1 Subjects Only)

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of investigational product. A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study. In the case of a positive confirmed pregnancy *after* administration of investigational product, the subject may remain in the study for blood sample collections and safety monitoring.

7.2. Biological Samples

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

The subject (subject's parent) may request that her samples (child's samples), if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other

researchers as long as confidentiality is maintained and no testing of the subject's genetic material is performed.

7.3. Immunogenicity

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

7.3.1. GBS Antibody Testing

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

CCI

7.3.3. Assessment of Antibody Responses to Routine Pediatric Vaccines in Infant Subjects

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

CCI [redacted]

7.5. Safety Parameters

Safety parameters will be assessed as described in the schedule of activities, Section 6, and below.

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

The safety parameters include e-diary reports of local reactions and systemic events that occur in the 7 days after investigational product administration. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 7.5.2.

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

In addition, AEs, MAEs, and SAEs are collected, recorded, and reported as defined in Section 8.

7.5.1. Subject Electronic Diary

The subject will be asked to monitor and record local reactions, systemic events, including fever, and antipyretics/pain medication used to prevent and/or treat symptoms, within a fixed time window each day for 7 days following vaccination (where Day 1 is the day of vaccination) on a system that uses a personal digital assistant (PDA) or other technology. In Stages 2 and 3, a baseline assessment (nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, or joint pain over the previous month) prior to vaccination will be recorded in the e-diary. This system, hereafter referred to as the subject's e-diary, allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Data on local reactions, systemic events, and antipyretics/pain medication used to prevent and/or treat symptoms

reported on the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting. These data do not need to be reported by the investigator in the CRF. However, if a subject withdraws because of prompted events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

Investigators (or appropriately qualified designee) are required to review the e-diary data online to evaluate subject compliance and as part of the ongoing safety review (see Stopping Rules in Section 7.7).

The investigator or designee must contact the subject in order to obtain stop dates for any reactions ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

7.5.2. Grading Scale for Prompted Events

The grading scales used in this study to assess AEs as described below are based on concepts outlined in the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[63]

7.5.2.1. Local Reactions

From Day 1 to Day 7, where Day 1 is the day of vaccination, subjects will be asked to assess pain at the injection site, redness, and swelling and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21+), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 4 below. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the subject as mild, moderate, or severe according to the grading scale in Table 4 below. A subject 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 subject's local reaction as Grade 4, after physical examination of the subject 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 subject. If a subject experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the subject regarding signs and symptoms that would prompt site contact. The procedure for notification of the sponsor is provided in the study documentation.

If a local reaction persists beyond the end of the e-diary period following vaccination, the subject will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Table 4. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Grade 4[b]
Pain at injection site	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity[c]	Emergency room visit or hospitalization
Erythema/ Redness	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Induration/ Swelling	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

a. Subjects experiencing ≥ Grade 3 local reactions are to be seen by the study site.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the electronic diary but will be recorded as an AE on the case report form.
c. Prevents daily activity, ie, results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

7.5.2.2. Systemic Events

In Stages 2 and 3, prior to vaccination, on Day 1, a baseline assessment (nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain over the previous month) will be recorded in the e-diary. From Day 1 to Day 7, where Day 1 is the day of vaccination, subjects will be asked to assess nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the subject as mild, moderate, or severe according to the grading scale in Table 5 below. Subjects will also be instructed to contact site staff if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, or joint pain) within 7 days after vaccination. Study staff may also contact the subject to obtain additional information on Grade 3 events entered into the e-diary.

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

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

Table 5. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

a. Subjects experiencing ≥ Grade 3 systemic events are to be seen by the study site.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the electronic diary but will be collected as an AE on the case report form.
c. Prevents daily routine activity, ie, results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

7.5.2.3. Fever

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

Table 6. Ranges for Fever

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

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

7.5.3. Laboratory Tests

For Stage 2 sentinel-cohort subjects, the safety laboratory tests in Table 7 will be performed at times defined in the schedule of activities and Section 6 of the protocol.

Table 7. Laboratory Tests

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

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

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

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

7.6. Use of Antipyretic/Pain Medication

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

7.7. Stopping Rules

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7.8. Other Safety Monitoring

7.8.1. Adverse Events

AEs and SAEs reported outside of the e-diary are recorded and reported as described in Section 8.

7.8.2. Immediate Adverse Events

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

7.8.3. Medically Attended Adverse Events

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

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

7.8.4. Adverse Events of Special Interest

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

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

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

8. ADVERSE EVENT REPORTING

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

The term “subject” in this section refers to (1) nonpregnant subjects; (2) the maternal subject and her fetus; and after delivery (3) the maternal subject and (4) the infant subject.

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Vaccine Serious Adverse Event (SAE) Reporting Form to

Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the investigational product under study during pregnancy (for Stage 1 subjects only), and occupational exposure.

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

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

Events listed in the table above that require reporting to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section, Section 8.2.3). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the Vaccine SAE

Reporting Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

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

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

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal Section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the Vaccine SAE Reporting Form, in accordance with the Requirements section, Section 8.1, above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each nonpregnant subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 3, and from Visit 5 to Visit 7. Between Visit 3 and Visit 4, and between Visit 7 and Visit 9, only SAEs (including hospitalizations) and MAEs will be reported.

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

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

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

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

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

8.1.4.1. Stage 1

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

Immediate AEs will be reported as detailed in Section 7.8.2.

8.1.4.2. Stages 2 and 3 – Maternal Subjects

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

Immediate AEs will be reported as detailed in Section 7.8.2.

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

8.1.4.3. Stages 2 and 3 – Infant Subjects

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

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

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

Table 8. Time Period for Collecting AE/SAE Information

Safety Event	Stage 1	Stages 2 and 3 Maternal Subject	Stages 2 and 3 Infant Subject
Nonserious AE	Consent – Visit 3 Visit 5 – Visit 7	Consent – Visit 3	Visit 1 (birth) – Visit 3
SAE	Consent – Visit 4 Visit 5 – Visit 9	Consent – Visit 9	Visit 1 – Visit 7

Table 8. Time Period for Collecting AE/SAE Information

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

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

a. Study procedures will only be performed in Stage 1 during the standard AE/SAE reporting period, thus AEs related to study procedures are not applicable. Therefore, during Stage 1, these events will be reported as per standard AE reporting requirements detailed in Section 8.1.4.1.

8.1.4.4. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the Vaccine SAE Reporting Form and the Exposure During Pregnancy Supplemental Form (Stage 1 subjects only), if applicable.

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

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

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

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

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

8.1.4.5. Recording Nonserious AEs and SAEs on the CRF

All AEs/SAEs occurring in a subject during the active collection period are recorded in the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

The investigator obtains general information on the pregnancy and its outcome for all study subjects. The investigator will follow the pregnancy until completion (or until pregnancy termination). In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, including miscarriage and missed abortion, intrauterine fetal demise, neonatal death [defined as those deaths that occur within 1 month of birth], or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should record this information in the CRF. In addition, infant deaths after 1 month of age should be recorded in the CRF as SAEs.

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study for subjects enrolled in Stage 1 or the expanded cohorts for Stage 2 and Stage 3. However, should an investigator deem it necessary to assess LFTs because a subject presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase, and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous

analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

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

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

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

Exposure to the investigational product under study during pregnancy or breastfeeding (applicable only to Stage 1 subjects) and occupational exposure (applicable to subjects in all study stages) are reportable to Pfizer Safety within 24 hours of investigator awareness. Refer to Section 8.1 for further details.

8.4.3.1. Exposure During Pregnancy

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

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

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

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

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

8.4.3.2. Exposure During Breastfeeding

Exposure during breastfeeding reports are not expected for maternal subjects who breastfeed a child delivered during the study.

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the Vaccine SAE Reporting Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant subject experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the Vaccine SAE Reporting Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Other examples include, but are not limited to:

- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

Such medication errors occurring to a study subject are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Reporting Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and additional details will be documented in the statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

All analyses for both immunogenicity and safety data will be descriptive in nature.

9.1. Sample Size Determination

This is a Phase 1/2 randomized, placebo-controlled, observer-blinded study to assess safety, tolerability, and immunogenicity of GBS6 in healthy nonpregnant as well as pregnant women and their infant subjects. The study consists of 3 stages. The sample sizes at each stage are not driven by any specific hypothesis testing.

Approximately 66 nonpregnant women will be enrolled at Stage 1, 22 subjects per group to receive placebo (saline control) or GBS6 (20 µg CPS/serotype/dose) with or without $AlPO_4$. Subjects in Stage 1 will also receive a booster dose of GBS6 (20 µg CPS/serotype/dose with $AlPO_4$) approximately 2 years after the initial dose of investigational product. Sample size for the subjects receiving GBS6 booster dose is dependent upon the number of subjects providing consent to continue in the study.

Approximately 360 pregnant women will be enrolled at Stage 2, 40 subjects at each GBS6 dose/formulation and a total of 120 subjects in the placebo group. Refer to Table 2 for a detailed description of the number of subjects per group. Approximately 160 pregnant women will be enrolled at Stage 3, 80 subjects at the selected GBS6 dose/formulation and 80 subjects in the placebo group. Enrollment will be monitored to help ensure distribution of vaccination across the gestational age range of ≥24 0/7 to ≤35 6/7 weeks.

Table 9 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 14 subjects in each dose/formulation group, there is 77% probability of observing at least 1 AE.

Table 9. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Sample Size (N)	Assumed True Event Rate of an AE					
	1.0%	2.0%	2.5%	3.0%	5.0%	10.0%
14	0.13	0.25	0.30	0.35	0.51	0.77
22	0.20	0.36	0.43	0.49	0.68	0.90
28	0.25	0.43	0.51	0.57	0.76	0.95
40	0.33	0.55	0.64	0.70	0.87	0.99
44	0.36	0.59	0.67	0.74	0.90	0.99
80	0.55	0.80	0.87	0.91	0.98	>0.99
120	0.70	0.91	0.95	0.97	>0.99	>0.99
240	0.91	0.99	>0.99	>0.99	>0.99	>0.99
320	0.96	>0.99	>0.99	>0.99	>0.99	>0.99

Abbreviations: $AlPO_4$ = aluminum phosphate; CPS = capsular polysaccharide.
Note: In Stage 1, 44 nonpregnant women are planned to be vaccinated with GBS6 (20 µg CPS/serotype/dose) with or without $AlPO_4$ (22/formulation). In each sentinel cohort of Stage 2, 28 maternal subjects are planned to be vaccinated with each dose of GBS6 with or without $AlPO_4$ (14/formulation). In Stage 2, a total of 80 maternal subjects are planned to be vaccinated with each dose of GBS6 with or without $AlPO_4$ (40/formulation), and a total of 240 maternal subjects are to be vaccinated with any dose of GBS6 with or without $AlPO_4$ (120/formulation). In the entire study, 320 maternal subjects are to be vaccinated with any dose of GBS6.

9.2. Immunogenicity Analysis

Immunogenicity data will be analyzed separately for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3), and their infant subjects (Stages 2 and 3). In addition, immunogenicity results from Stages 2 and 3 will be combined for analysis for maternal subjects as appropriate, and also combined for their infant subjects.

9.2.1. Immunogenicity Analysis Populations

For the immunogenicity analyses, 2 analysis populations will be defined separately for nonpregnant women, maternal subjects, and their infant subjects: evaluable immunogenicity and modified intent-to-treat (mITT) populations.

For the immunogenicity analyses, nonpregnant and maternal subjects will be analyzed according to the investigational product received for the evaluable immunogenicity population and the investigational product as randomized for the mITT population. Infant subjects will be analyzed according to the investigational product received by their mothers (maternal subjects) for the evaluable immunogenicity population and the investigational product assigned to their mothers (maternal subjects) for the mITT population. The evaluable immunogenicity population is considered to be the primary population for the immunogenicity analyses.

9.2.1.1. Nonpregnant Women (Stage 1)

To be included in the evaluable immunogenicity population of primary vaccination, in general, a Stage 1 subject must have been eligible for the study, have received GBS6 or placebo as randomized, have had blood drawn within the specified time frames, have had at least 1 valid and determinate assay result for the proposed analysis, and have had no other major protocol violations. To be included in the mITT population, a Stage 1 subject must be randomized and have had at least 1 valid and determinate assay result related to the proposed analysis.

To be included in the evaluable immunogenicity population of booster vaccination, in general, a Stage 1 subject must have been eligible for the study, have received a booster dose of GBS6, have had blood drawn within the specified time frames, have had at least 1 valid and determinate assay result for the proposed analysis, and have had no other major protocol violations. To be included in the mITT population, a Stage 1 subject must have at least 1 valid and determinate assay result related to the proposed analysis.

9.2.1.2. Maternal Subjects (Stages 2 and 3)

Similarly, to be included in the evaluable immunogenicity population, a maternal subject from Stage 2 or 3 must have been eligible for the study, have received GBS6 or placebo as randomized, have had blood drawn within the specified time frames, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations. To be included in the mITT population, a maternal subject from Stage 2 or 3 must be randomized and have at least 1 valid and determinate assay result related to the proposed analysis.

9.2.1.3. Infant Subjects (Stages 2 and 3)

To be included in the evaluable immunogenicity population, an infant subject from Stage 2 or 3 must have been eligible for the study, the infant subject's mother must have received GBS6 or placebo as randomized, and the infant subject must have had blood drawn within the specified time frames, have at least 1 valid and determinate assay result for the proposed analysis, and have no other major protocol violations. To be included in the mITT population, the infant subject's mother must be randomized and the infant subject must have at least 1 valid and determinate assay result related to the proposed analysis.

9.2.2. Analysis of Immunogenicity Endpoints

Immunogenicity endpoints are secondary CCI [redacted] in the study as listed in Section 2.2. Descriptive summary statistics will be provided for all immunogenicity endpoints. No formal between-group comparison will be made.

Descriptive evaluations include GBS6 serotype-specific IgG GMCs and OPA GMTs measured at prespecified time points and will be summarized by vaccine group.

GBS6 serotype-specific IgG concentrations will be logarithmically transformed for analysis. For each serotype, GMCs will be calculated at all blood draw visits. Two (2)-sided 95% confidence intervals (CIs) for the GMCs will be constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using Student's t distribution.

OPA GMTs and the corresponding 2-sided 95% CIs for the GBS6 serotype-specific OPA titers will be computed using similar methods to those for IgG concentrations.

The proportions of subjects achieving defined GBS6 serotype-specific IgG concentrations and OPA titers will be summarized descriptively at prespecified time points as counts and percentages with 2-sided 95% exact CIs by vaccine group.

CCI [redacted]

All of the binary endpoints will be descriptively summarized with 2-sided exact 95% CIs using the Clopper-Pearson method.

Reverse cumulative distribution curves (RCDCs) for combination of prespecified time points and vaccine groups will be generated for each GBS6 serotype. Additionally, antibody response line plot of geometric means and the associated 95% CIs will be presented at each analysis time point by vaccine group and serotype.

Detailed analyses of all the immunogenicity endpoints CCI [redacted] and graphical displays will be described in the SAP.

9.3. Safety Analysis

Safety data will be analyzed separately for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3), and their infant subjects (Stages 2 and 3).

9.3.1. Safety Population

A safety population will be defined separately for nonpregnant women, maternal subjects, and their infant subjects.

For the safety analyses, nonpregnant and maternal subjects will be analyzed according to the investigational product received and infant subjects will be analyzed according to the investigational product their mothers (maternal subjects) received.

9.3.1.1. Nonpregnant Women (Stage 1)

All Stage 1 subjects receiving a primary dose of GBS6 or placebo will be included in the safety population of primary vaccination.

All Stage 1 subjects receiving a booster dose of GBS6 will be included in the booster safety population.

9.3.1.2. Maternal Subjects (Stages 2 and 3)

All maternal subjects from Stages 2 or 3 receiving a dose of GBS6 or placebo will be included in the safety population.

9.3.1.3. Infant Subjects (Stages 2 and 3)

All infant subjects who are enrolled in the study will be included in the safety population.

9.3.2. Analysis of Safety Endpoints

The safety endpoints as listed in Section 2.1 are primary in the study and their analyses are based on the safety population.

The safety analyses for Stage 1 nonpregnant women and maternal subjects from Stages 2 and 3 are descriptive evaluations of local reactions, systemic events, AEs, MAEs, and SAEs by vaccine group. In addition, clinical laboratory abnormalities, delivery outcomes, and obstetric complications for maternal subjects from Stages 2 and 3 will be summarized by vaccine group. The safety analyses for infant subjects from Stages 2 and 3 are descriptive evaluations of birth outcomes, AEs, MAEs, AEs of special interest, and SAEs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).

Descriptive summary statistics for continuous outcomes will include number of subjects, mean, standard deviation, median, minimum, and maximum and 2-sided 95% CIs for the mean, as needed. For categorical outcomes, number and percentage of subjects in each category and 2-sided 95% exact CIs using Clopper-Pearson method will be provided.

9.4. Analysis Timing

In addition to the planned safety data review while the study is ongoing, 4 interim analyses are planned for this study.

The first interim analysis will be performed when 1-month postvaccination safety data from all subjects enrolled in Stage 1 are available. Stage 2 of the study will be initiated based on results from the first interim analysis as well as those from the 1-month postvaccination safety and immunogenicity data of 3 different dose levels of GBS6 formulated with or without $AlPO_4$ from the prior US FIH Phase 1/2 study (C1091001). Both the IRC and E-DMC will review all the available unblinded data and the IRC in consultation with the E-DMC will make the recommendations regarding the study proceeding to Stage 2. For details of sponsor blinding, refer to Section 5.8.

The second interim analysis will be performed when delivery/birth safety and immunogenicity data from all maternal subjects in the sentinel cohorts and their infant subjects in Stage 2 are available. Safety and immunogenicity data from all maternal sentinel-cohort study subjects and their infants will be included in the analysis. The second interim analysis is being conducted for internal planning purposes only. These unblinded data will be reviewed by the IRC. For details of sponsor blinding, refer to Section 5.8.

The third interim analysis will be performed when delivery/birth safety and immunogenicity data from all maternal subjects and their infant subjects in Stage 2 are available. All available safety and immunogenicity data from all study subjects will be included in the analysis. The primary objective of the third interim analysis is to select a dose and formulation for Stage 3. These unblinded data will be reviewed by the IRC. The final GBS6 dose and formulation to take into Stage 3 and further development will be selected after this review. For details of sponsor blinding, refer to Section 5.8.

The fourth interim analysis will be performed when delivery/birth safety and immunogenicity data from all maternal subjects and their infant subjects in Stage 3 are available. All available safety and immunogenicity data from all study subjects will be included in the analysis. The primary objective of the fourth interim analysis is to support internal development decisions and potential regulatory agency interactions for the program. These unblinded data will be reviewed by the IRC. For details of sponsor blinding, refer to Section 5.8.

No multiplicity adjustments will be applied for these assessments.

After the completion of the 12-month postdelivery/birth follow-up visit for subjects in Stage 3, a clinical study report (CSR) including all unblinded safety and immunogenicity data gathered from all subjects from each of the 3 stages will be issued. Safety and immunogenicity data from subjects who receive the same vaccine dose/formulation or placebo in Stages 2 and 3 will be combined and analyzed together for maternal subjects and also analyzed together for their infant subjects.

Safety and immunogenicity data from infant subjects who are born to maternal subjects receiving the same vaccine dose/formulation or placebo in Stages 2 and 3 will be combined and analyzed together.

9.5. Data Monitoring Committee

This study will use both an IRC and an E-DMC.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter, as well as the analysis results with the safety data cutoff at 1 month after vaccination for subjects from Stage 1 as described in Section 9.4 above. The E-DMC will also meet for an ad hoc safety review should enrollment of Stage 2 subjects be halted, to review the IRC recommendation and make a recommendation before enrollment may be restarted, the protocol modified, or enrollment terminated. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

The E-DMC will not participate in the Stage 2 dose-escalation processes, but will participate in the stopping rule and overall safety data review processes, in line with the remit of the E-DMC charter.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed ICDs, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICDs, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), the ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the CSA and applicable privacy laws. The ICDs and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The ICDs used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or parent(s) if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study, and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject, or parent(s) if a minor, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a subject's parent(s), the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent.

Before any study-specific activity is performed, the investigator, or a person designated by the investigator, will obtain written informed consent from each maternal subject. This will include written informed consent for the mother and the fetus during the pregnancy, and the infant subject's continuation in the study after delivery. Informed consent will be obtained from the father of the fetus/infant subject if mandated by local requirements.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of GBS6 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 30 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
$AlPO_4$	aluminum phosphate
ALT	alanine aminotransferase
Apgar	appearance, pulse, grimace, activity, and respiration
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
CK	creatine kinase
CPS	capsular polysaccharide
CRF	case report form
CRM_{197}	cross-reactive material 197
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
dLIA	direct Luminex immunoassay
EC	ethics committee
EDD	estimated delivery date
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOD	early-onset disease
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FIH	first-in-human
FSH	follicle-stimulating hormone
GA	gestational age
GBS	group B streptococcus
GBS6	group B streptococcus 6-valent polysaccharide conjugate vaccine
GBS III-TT	group B streptococcus type III capsular polysaccharide-tetanus toxoid conjugate vaccine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation	Term
GMC	geometric mean concentration
GMT	geometric mean titer
HBV	hepatitis B virus
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IAP	intrapartum antibiotic prophylaxis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive Web-based response
LFT	liver function test
LMIC	low- and middle-income country
LMP	last menstrual period
LOD	late-onset disease
LSLV	last subject last visit
MAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NaCl	sodium chloride
OPA	opsonophagocytic activity
PDA	personal digital assistant
PI	principal investigator
PT	prothrombin time
RBC	red blood cell
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document

Abbreviation	Term
TBili	total bilirubin
Tdap	tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine
ULN	upper limit of normal
US	United States
WBC	white blood cell

Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
PPD	25-Nov-2020 13:26:30	Author Approval
PPD	25-Nov-2020 14:45:22	Final Approval

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 2

Version: 3.0

Date: 17-May-2021

Prepared By: PPD PhD, PPD

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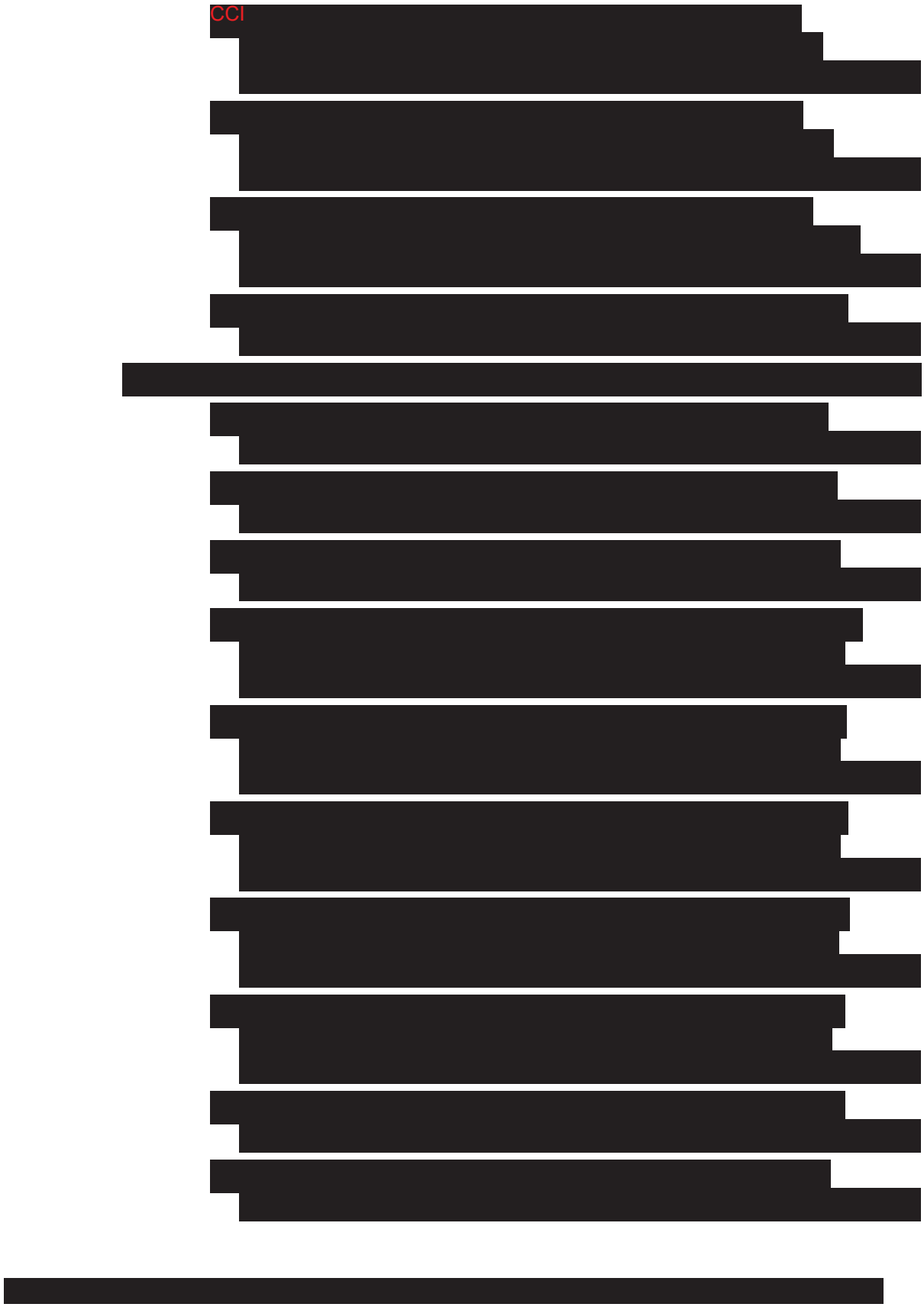

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Protocol C1091002

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

Version: 1.0

Date: 21-DEC-2018

Prepared By: PPD , PhD, PPD

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C1091002 is based on the final protocol dated 11MAY2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1.0	Not Applicable	Not Applicable

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 GBS6 formulations in healthy nonpregnant women 18 to 40 years of age.

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 subjects 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 27 to 36 weeks' gestation.

- To assess the safety of maternal immunization in infant subjects 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.

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 level/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 subjects delivered to maternal subjects vaccinated with GBS6.

- To assess placental transfer of antibody from maternal subjects vaccinated with GBS6 to their infant subjects.

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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 GBS vaccine in healthy 18 to 40 year-old nonpregnant women and pregnant women vaccinated between 27 0/7 and 35 6/7 weeks' gestation and their infant subjects. A total of approximately 586 subjects (66 nonpregnant women and 520 maternal subjects 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 subjects enrolled/group) to receive placebo (saline control) or GBS6 (20 µg CPS/serotype/dose) with or without $AlPO_4$.

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 subject through 14 days after vaccination) of the sentinel cohort of subjects at each dose level. Pregnant women, once consented, will be referred to as "maternal subjects." The first 42 eligible maternal subjects at each dose level will compose a sentinel cohort. Starting with the lowest dose level, maternal subjects will be randomly assigned (in a 1:1:1 ratio, 14 subjects 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 subjects are enrolled (expanded cohort).

Approximately 360 maternal subjects are planned to be enrolled into Stage 2 (see Table 2).

2.2.3. Stage 3

Approximately 160 additional maternal subjects will be enrolled in Stage 3, to receive a single dose/formulation of the selected GBS6 or placebo (saline control) in a 1:1 ratio.

Table 2. Planned Subjects: Total and Number in Each Stage and Group

Stage 1 Dose/Formulation Group		Total (1:1:1)		
Highest Dose[a]	GBS6 (20 µg CPS/serotype/dose) with $AlPO_4$	22		
	GBS6 (20 µg CPS/serotype/dose) without $AlPO_4$	22		
	Placebo (saline control)	22		
Stage 2 Dose/Formulation Groups		**Sentinel (1:1:1)**	**Expanded (1:1:1)**	**Total**
Lowest Dose	GBS6 lowest dose with $AlPO_4$	14	26	40
	GBS6 lowest dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[b]
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[b]
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[b]
Stage 3 Dose/Formulation Group		**Total (1:1)**		
Selected Dose	Selected GBS6 dose/formulation	80		
	Placebo (saline control)	80		

Abbreviations: $AlPO_4$ = aluminum phosphate; CPS = capsular polysaccharide; FIH = first-in-human.

a. One hundred four healthy adults (males and females) aged 18 to 49 years have received this dose level (~52/formulation with/without $AlPO_4$) in the US FIH Phase 1/2 study (C1091001).

b. Approximately 120 pregnant control subjects 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 the protocol Section 3.

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 investigational product (pain at the injection site, redness, and swelling).

- Proportions of nonpregnant women 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 nonpregnant women reporting adverse events (AEs) through 1 month following administration of investigational product.

- Proportions of nonpregnant women reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) through 6 months following administration of investigational product.

3.1.2. Primary Endpoints: Maternal Subjects (Stages 2 and 3)

- Proportions of sentinel-cohort maternal subjects (Stage 2 only) with clinical laboratory abnormalities following administration of investigational product at the 2-week follow-up visit.

- Proportions of maternal subjects reporting prompted local reactions within 7 days following administration of investigational product (pain at the injection site, redness, and swelling).

- Proportions of maternal subjects 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 subjects reporting AEs through 1 month after administration of investigational product.

- Proportions of maternal subjects with SAEs, MAEs, and obstetric complications (prepartum, intrapartum, and postpartum) throughout the study (Visit 1 through the 12-month after delivery study visit).

- Proportions of maternal subjects with each delivery outcome and delivery mode.

3.1.3. Primary Endpoints: Infant Subjects (Stages 2 and 3)

- Proportions of infant subjects with specific birth outcomes.

- Proportions of infant subjects with AEs from birth to 6 weeks of age.

- Proportions of infant subjects 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)

- GBS serotype-specific IgG geometric mean concentrations (GMCs) 1 month after vaccination in nonpregnant women.

- GBS serotype-specific OPA geometric mean titers (GMTs) measured 1 month after vaccination in nonpregnant women.

3.2.2. Secondary Endpoints: Maternal Subjects (Stages 2 and 3)

- GBS serotype-specific IgG GMCs measured at 2 weeks and 1 month after vaccination and at delivery in maternal subjects.
- GBS serotype-specific OPA GMTs measured at 2 weeks and 1 month after vaccination and at delivery in maternal subjects.

3.2.3. Secondary Endpoints: Infant Subjects (Stages 2 and 3)

- GBS serotype-specific IgG GMCs in infant subjects measured at birth.
- GBS serotype-specific OPA GMTs in infant subjects measured at birth.

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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 and systemic reactions in the electronic diary (e-diary).

Day 1 is considered the baseline visit for the following assessments: Immunogenicity, CCI [redacted] and vital signs.

Maternal Subjects: 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 Subjects: Stage 2 Sentinel Cohort

Laboratory (hematology and chemistry) data will be collected for sentinel cohort maternal subjects only. Data is collected during the screening visit, Visit 0 (-14 to -2 days prior to vaccination) and will be considered baseline data. For subjects with a rescreening visit, the rescreening laboratory results will be considered as the baseline data.

Infant Subjects: Stages 2 and 3

Day 1 is defined as the day of birth (Visit 1) for the infant subjects that corresponds to Visit 4 (delivery visit) for maternal subjects.

Day 1 is considered the baseline visit for the following assessments: Immunogenicity, CCI [redacted], physical exam and vital signs.

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 one category is selected for race, the subject 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 one day before the subject's 19th birthday, the subject is 18 years old.

Medical history of clinical significance will be collected and categorized according to the current version (at time of reporting) of the Medical Dictionary of Regulatory Activities (MedDRA).

3.4.2. Demographics, Substance Use, Medical History and Obstetric History: Maternal Subjects (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 one day before the subject's 19th birthday, the subject 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 time of reporting) of the Medical Dictionary of Regulatory Activities (MedDRA).

Obstetric history of clinical significance including history from prior and current pregnancy (ies) will be collected that includes the following: number of previous pregnancies, live births, still deliveries, vaginal deliveries, C-sections, spontaneous abortions, elective

terminations, ectopic pregnancies, previous neonatal deaths and number of pregnancies that results 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 caesarean section (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), post-partum 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 performed and recorded at 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 Subjects (Stages 2 and 3)

Demography data collected at birth include sex, race, ethnicity, racial designation and date of birth and time. Data on feeding modality (breast milk only, formula only, mixed feeding) will be collected at each after birth timepoint.

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3.6. Safety Endpoints

3.6.1. Adverse Events

All AEs are collected on the case report form (CRF) for nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) and will be categorized according to the current version (at time of reporting) of the Medical Dictionary of Regulatory Activities (MedDRA).

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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 subjects (Stages 2 and 3) (see Section 7.8.2 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 (Stage 1) subjects, from screening up to Visit 9 for maternal subjects (Stages 2 and 3), and up to Visit 7 for infant subjects (Stages 2 and 3).

AEs of special interest for infant subjects (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 after birth visit). GBS infections that occurred during Days 1-7 are referred to as early onset (EOD) and those that occurred during Days 8-90 are referred to as late onset (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 8.1.4 (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 pre-identified tier-1 events for this study.

- Tier-2 events: These are events that are not tier-1 but are "common." A MedDRA preferred term (PT) is defined as a tier-2 event if there are 4 or more subjects in at least one 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 subjects (Stages 2 and 3) during Days 1-7, starting on the day of the vaccination [Day 1 (Visit 1)].

3.6.2.1. Local Reactions

Local reactions reported in the e-diary are pain at injection site, redness, and swelling.

Presence of Local Reactions (Proportion of Subjects Reporting)

The subject will record the presence or absence of pain at injection site in the e-diary as 'Mild', 'Moderate', 'Severe' or 'None'. The presence or absence of redness or swelling to be recorded as 'Yes' or 'No'. Additionally, if redness or swelling is present, then the subject

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 subject 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 subject's local reaction as Grade 4, after physical examination of the subject or documentation from another medically qualified source (e.g., emergency room or hospital record), or, in the case of pain at the injection site only, telephone contact with the subject. If a subject experiences a Grade 4 local reaction, it will be captured as an adverse event 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 for in the analysis.

The presence or absence of each local reaction on a given day is defined as follows:

= missing if value is missing on a given day;

= 'Yes', if the subject reports the reaction as 'Yes' for redness or swelling **or** 'Mild', 'Moderate' or 'Severe' or 'Grade 4' for pain at injection site on a given day;

= 'No' if the subject reports the reaction as 'No' for redness or swelling **or** 'None' for pain at injection site on a given day.

For each local reaction, the derivation of whether or not the specific reaction occurred on "any Day 1-7" will be made. The derivation of this variable is given in Table 3 below.

Table 3. Derived Variables for Each Local Reaction

Variable[a]	Yes (1)	No (0)	Missing (.)
Any Day 1-7	Subject reports the reaction as 'Yes' on any Day 1-7	Subject reports the reaction as 'No' on all 7 days or as a combination of 'No' and missing on all 7 days.	Subject 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 below.

Table 4. Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
Any Day 1-7	Subject reports any local reaction as 'Yes' on any day during Days 1-7	Subject 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.	Subject reports all of the local reactions as missing on all 7 days.

[redacted]

[redacted]

Grading Scale for Local Reactions

The grading of local reactions is listed below 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. Subjects 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, i.e., 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 1-7;

= 0, if the subject reports all reactions as 'No' or a combination of missing and "No" for all 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 in which the event is recorded in the e-diary or the date the event ends if it is unresolved during the subject 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. Subjects 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 subjects 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 reaction:

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 1-7" after vaccination.
3. Maximum severity of each local reaction on "any Day 1-7" after vaccination.
4. Presence or absence of any local reaction on "any 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 Days 1-7 data, prior to vaccination on Day 1, a baseline assessment of systemic events will be recorded in the e-diary for the maternal subjects (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 to be 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 subject to document the presence or absence of remaining systemic events in the e-diary as 'Mild', 'Moderate', 'Severe' or 'None'. Subjects to be asked to assess severity of each event according to the Table 6 below. Study staff may also contact the subject to obtain additional information on Grade 3 events entered into the e-diary. Only an investigator is able to classify a subject's systemic event as Grade 4, after physical examination of the subject or documentation from another medically qualified source (e.g., emergency room or hospital record), or telephone contact with the subject. If a subject 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 101.15°F)
- >38.5°C to 38.9°C (>101.15°F to 102.05°F)
- >38.9°C to 40.0°C (>102.05°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: IV = intravenous.

a. Subjects 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 event will not be collected in the e-diary but will be recorded as an AE on the CRF.
c. Prevents daily routine activity, i.e., 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 subject reports a temperature ≥38.0°C for fever **or** 'Mild', 'Moderate' or 'Severe' or 'Grade 4' for the remaining events on a given day;

= 'No' if the subject reports a temperature <38.0°C 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 1-7" after vaccination.
3. Maximum severity of each systemic event on "any Day 1-7" after vaccination.
4. Presence or absence of any systemic event on "any 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 similar to the derived variables for local reaction:

1. Use of antipyretic/pain medication on each day (Days 1-7) after vaccination.
2. Use of antipyretic/pain medication on "any 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 subjects (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 below in Table 7.

Table 7. Laboratory Tests

Hematology	Chemistry
Hemoglobin	BUN and Creatinine
Hematocrit	AST, ALT
RBC count	Total bilirubin
Platelet count	Alkaline phosphatase
WBC count	
Total neutrophils (Abs)	
Eosinophils (Abs)	
Monocytes (Abs)	
Basophils (Abs)	
Lymphocytes (Abs)	

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = while blood cell.

The toxicity grading scale in Table 8 below for pregnant women will be adapted, as appropriate at a specific timepoint (e.g. 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 – 28 0/7 weeks gestation and third trimester as 28 1/7 weeks gestation to delivery.

Table 8. Hematology and Blood Chemistry Toxicity Grading Scale

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Female Hemoglobin (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
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[a] 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[a] 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

[redacted]

[redacted]

Table 8. Hematology and Blood Chemistry Toxicity Grading Scale

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
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		
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
Blood urea nitrogen (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
Aspartate aminotransferase (AST[b]) U/L	Second Trimester	3-33	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c] cirrhosis transplant candidate
	Third Trimester	4-32	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c] cirrhosis transplant candidate
Alanine aminotransferase (ALT[d]) U/L	Second Trimester	2-33	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>10 x ULN[c]
	Third Trimester	2-25	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c] cirrhosis transplant candidate
Total bilirubin (with increased LFTs) mg/dL	Second Trimester	0.1-0.8	>1.0-1.2 x ULN[c]	>1.2-1.5 x ULN[c]	>1.5-1.8 x ULN[c]	>1.8 x ULN[c]
	Third Trimester	0.1-1.1	>1.0-1.2 x ULN[c]	>1.2-1.5 x ULN[c]	>1.5-1.8 x ULN[c]	>1.8 x ULN[c]

Table 8. Hematology and Blood Chemistry Toxicity Grading Scale

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
Total bilirubin (with normal LFTs) mg/dL	Second Trimester	0.1-0.8	>1.0-1.5 x ULN[c]	>1.5-2.0 x ULN[c]	>2.0-3.0 x ULN[c]	>3.0 x ULN[c]
	Third Trimester	0.1-1.1	>1.0-1.5 x ULN[c]	>1.6-2.0 x ULN[c]	>2.0-3.0 x ULN[c]	>3.0 x ULN[c]
Alkaline phosphatase U/L	Second Trimester	25-126	1.1-2.0 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c]
	Third Trimester	38-229	>1.0-1.2 x ULN[c]	>1.2-3.0 x ULN[c]	>3.0-8.0 x ULN[c]	>8.0 x ULN[c]

a. WBC = white blood cell
b. AST = aspartate aminotransferase
c. ULN = upper limit of normal
d. ALT = alanine aminotransferase

3.6.4. Physical Examinations, Including Vital Signs

3.6.4.1. Physical Examinations, Including Vital Signs: Nonpregnant Women (Stage 1)

Physical examination will be performed at screening visit (Visit 0) and 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 screening visit (Visit 0) and prior to vaccination on Day 1 (Visit 1) and recorded in the CRF.

3.6.4.2. Physical Examinations, Including Vital Signs: Maternal Subjects (Stages 2 and 3)

Physical examination will be performed at 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), 2-Week follow-up (Visit 2), 1-Month follow-up (Visit 3) and 6-Week after delivery visits (Visit 6). Abnormal results, including those that indicate worsening of medical history conditions, will be recorded in the AE CRF.

Vital signs including weight, height, sitting systolic and diastolic blood pressure, pulse rate, respiratory rate and oral temperature will be measured at screening visit (Visit 0), prior to vaccination on Day 1 (Visit 1), 2-Week follow-up (Visit 2) and 1-Month follow-up (Visit 3) and recorded in the CRF.

3.6.4.3. Physical Examinations, Including Vital Signs: Infant Subjects (Stages 2 and 3)

Physical examination will be performed at birth (Visit 1), 6-Week after delivery (Visit 3), 14-Week after delivery (Visit 4), 18-Week after delivery (Visit 5) and 12-Month after

delivery (Visit 7) visits 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-Week after delivery (Visit 3), 14-Week after delivery (Visit 4), 18-Week after delivery (Visit 5) and 12-Month after delivery (Visit 7) visits and recorded in the CRF.

3.6.5. Obstetric Examinations and Pregnancy Outcome: Maternal Subjects (Stages 2 and 3)

Obstetric examination findings will be collected at screening (Visit 0) through 1-Month follow-up visit (Visit 3) and includes 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 exam status (normal, abnormal), fundal height (cm), fetus 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), pathology performed (yes, no).

3.6.6. Birth Outcome: Infant Subjects (Stages 2 and 3)

Infant outcome at birth will be collected at the delivery visit and includes 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, stillbirth, neonatal death) will be derived using the response to "delivery outcome" from the pregnancy outcome and the AE data. Neonatal death is defined as the death of a live born infant that occurred within a month of birth.

3.7. Study Conduct

3.7.1. E-diary Completion

On a specific day, the nonpregnant women and maternal subjects are expected to complete all the questions [the 3 local reactions, the 7 systemic events (including fever), and the use of antipyretic medication] in e-diary. In that case, e-diary data will be transmitted and

considered as complete. The data could be missing in the e-diary for a specific day, in which case it will not be transmitted and 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 (at time of reporting) 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 to 1-Month follow-up (Visit 3) will be recorded in the CRF.

Any medications taken from the signing of informed consent through 1-Month follow-up (Visit 3) will be recorded in the CRF. Additionally, any medication taken to treat AEs from the signing of the informed consent through 6-Month follow-up (Visit 4) will be recorded in the CRF.

3.7.2.2. Nonstudy Vaccines and Concomitant Treatments: Maternal Subjects (Stages 2 and 3)

Any nonstudy vaccinations given from the signing of the informed consent to delivery (Visit 4) will be recorded in the CRF.

Any medications taken from the signing of informed consent through 1-Month follow-up (Visit 3) will be recorded in the CRF. Antibiotic treatment taken from the signing of informed consent to 12-Month after delivery follow-up (Visit 9) will be recorded. Additionally, any medication taken to treat AEs from the signing of the informed consent through 12-Month after delivery follow-up (Visit 9) will be recorded in the CRF.

3.7.2.3. Nonstudy Vaccines and Concomitant Treatments: Infant Subjects (Stages 2 and 3)

Any nonstudy vaccinations received from birth (Visit 1) to 12-Month after birth follow-up (Visit 7) will be recorded in the CRF.

Any medications taken from birth (Visit 1) through 6-Week after delivery follow-up (Visit 3) will be recorded in the CRF. Antibiotic treatment taken from birth to 12-Month after birth follow-up (Visit 7) will be recorded. Additionally, any medication taken to treat AEs from birth through 12-Month after delivery follow-up (Visit 7) will be recorded in the CRF.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects 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 subjects, and their infant subjects: 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 subjects (Stage 2) 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 subjects (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 evaluable immunogenicity population will include subjects 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 a Visit 3 (1 month after vaccination) blood drawn for assay testing within 27 to 49 days, inclusive, after vaccine administration;
- Have at least one valid and determinate assay result for the 1 month after vaccination visit;
- Has 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, e.g., subject 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 subjects with protocol violations before any immunogenicity analysis is carried out.

4.1.2. Per Protocol Analysis Set: Maternal Subjects (Stages 2 and 3)

The evaluable immunogenicity population will include subjects 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 at Visit 3 (1 month after vaccination) within 27 to 49 days, inclusive, after vaccine administration or at the delivery visit;
- Have at least one valid and determinate assay result for either the 1 month after vaccination or the delivery visit;
- Has 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 Subjects (Stages 2 and 3)

The evaluable immunogenicity population will include subjects who:

- Are eligible (have signed informed consent from the mother and met all inclusion/exclusion criteria) and mother was randomized into the study;
- Mother has received GBS6 or placebo as randomized;
- Have cord blood available or Visit 1 (birth) blood drawn for assay testing within 72 hours after birth;
- Have at least one valid and determinate assay result at the birth visit (Visit 1);
- Has 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 modified intent-to-treat (mITT) population.

The immunogenicity data based on the mITT population for nonpregnant women (Stage 1) and maternal subjects (Stage 2) will be summarized according to the vaccine group as randomized. The immunogenicity data for infant subjects (Stages 2 and 3) will be summarized according to the vaccine group as randomized to their mothers.

The immunogenicity results based on mITT population will be summarized for secondary immunogenicity endpoint(s) within each stage of the study only if there is a sizable difference (e.g. ~ 10%) in the number of subjects between the mITT and the evaluable

immunogenicity populations. CCI [redacted]

4.2.1. Full Analysis Set: Nonpregnant Women (Stage 1)

All randomized subjects who have at least one valid and determinate assay result will be included in the mITT population.

4.2.2. Full Analysis Set: Maternal Subjects (Stages 2 and 3)

All randomized subjects who have at least one valid and determinate assay result will be included in the mITT population.

4.2.3. Full Analysis Set: Infant Subjects (Stages 2 and 3)

All infants of randomized maternal subjects who have at least one 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, maternal subjects, and their infant subjects. The safety population is the analysis population for all the safety endpoints.

The safety data for nonpregnant women (Stage 1) and maternal subjects (Stage 3) will be summarized according to the vaccine group as administered. The safety data for infant subjects (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 subjects who received GBS6 vaccine or placebo injection will be included in the safety population.

4.3.2. Safety Analysis Set: Maternal Subjects (Stages 2 and 3)

All subjects who received GBS6 vaccine or placebo injection will be included in the safety population.

4.3.3. Safety Analysis Set: Infant Subjects (Stages 2 and 3)

All infants whose mother received GBS6 vaccine or placebo injection will be included in the safety population.

4.4. Other Analysis Sets

No other analysis sets will be defined in this study.

4.5. Treatment Misallocations

- Randomized but not vaccinated: this group includes nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) who were randomized but not vaccinated and infant subjects (Stages 2 and 3) whose mothers were randomized but not vaccinated. These subjects will not be included in the safety population for safety analyses. These subjects will not be included in the evaluable immunogenicity population, but they will be included in the mITT population for immunogenicity analyses for subjects with valid and determinant assay results. The immunogenicity results for these subjects will be reported under the vaccine group as randomized or their mothers randomized in case of infant subjects.

- Vaccinated but not randomized: this group includes nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) who were vaccinated but not randomized and infant subjects (Stages 2 and 3) whose mothers were vaccinated but not randomized. These subjects 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 vaccine received by their mothers in case of infant subjects. They will be excluded from immunogenicity analyses based on either evaluable immunogenicity or mITT populations.

- Randomized but received incorrect vaccine: this group includes nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) who were randomized but received incorrect vaccine and infant subjects (Stages 2 and 3) whose mothers were randomized but received incorrect vaccine. These subjects 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 subjects 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 subjects 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 subjects. 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, descriptive statistics for continuous variables are: n, mean, median, standard deviation, minimum and maximum. 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 Stage. In Stage 1, the subset will only include groups 5 thru 7; Stage 2 will include all vaccine groups; Stage 3 will include one vaccine group chosen from groups 1-6 and group 7. Unless otherwise explicitly stated, all Stage 2 maternal subjects from both sentinel and expanded cohorts will be combined, by vaccine groups listed above. Similarly, all Stage 2 infant subjects from both sentinel and expanded cohorts will be combined, according to their mother's vaccine group.

Both immunogenicity and safety results will be summarized separately for non-pregnant women (Stage 1), maternal subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3).

5.2.1. Analyses for Binary Data

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 subjects, then it follows that $p = r / n$ is the estimate of the proportion of responses. An exact 95% confidence interval can be computed by solving the following 2 equations. For the lower limit P_L, use

$$p_L = \frac{rF_L}{(rF_L + (n - r + 1))}$$

and for the upper limit P_U, use

$$p_U = \frac{(r+1)F_U}{(n-r) + (r+1)F_U}$$

where F_L is the quantile from the F distribution for α=0.025, with numerator degrees of freedom equal to 2r and denominator degrees of freedom equal to 2(n-r+1). F_U is the quantile from the F distribution for α=0.975, with numerator degrees of freedom equal to 2(r+1) and denominator degrees of freedom equal to 2(n-r). When r equals 0, F_L should be set equal to 1.0 so P_L equals 0. When r equals n, F_U should be set equal to 1.0 so P_U equals 1.

The CI using the F distribution is described in Collett, (1991)[3].

CCI [redacted]

[redacted]

[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 subjects reporting local reactions, systemic events (Stage 1 nonpregnant women, Stages 2 and 3 maternal subjects), AEs, SAEs, and MAEs (Stage 1 nonpregnant women, Stages 2 and 3 maternal subjects and their infants), obstetric complications, delivery outcomes and delivery mode (Stages 2 and 3 maternal subjects) and AEs of special interest (Stages 2 and 3 infant subjects).

For tier-2 AEs only, 95% CIs for the difference in proportions between each GBS vaccine group and placebo (risk difference) based on the Chan and Zhang[4] method will be provided for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3) and infant subjects (Stages 2 and 3).

[redacted]

[redacted]

5.2.2. Analyses for Continuous Data

5.2.2.1. Geometric Means (GMs)

The GBS6 serotype-specific IgG, CCI and OPA, CCI CCI antibody levels at selected blood sampling timepoints 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 (GMRs)

The GBS6 serotype-specific antibody level ratios of infant to mother IgG CCI will be summarized by vaccine group at birth/delivery blood sampling timepoint by geometric means and associated 2-sided 95% CIs. The antibody levels are logarithmically transformed for analysis. The 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 (RCDCs)

Empirical RCDCs will be presented graphically by plotting the proportion of subjects with the GBS6 serotype-specific antibody level equal to or exceeding the specified antibody level vs indicated antibody level for each serotype separately by vaccine group and at a specific blood sampling timepoint (e.g. 1 month after vaccination for nonpregnant women) for subjects from different stages. The RCDCs at other timepoints may be generated. The lower limit of quantitation (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 and OPA titers by vaccine group at before vaccination (Day 1) and after vaccination blood sampling timepoints for both nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3). Similarly for the

infant subjects (Stages 2 and 3) by their mother's vaccine group at birth and after birth blood sampling timepoints. 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-effect model for maternal and infant subjects with repeated measurements (MMRM)[5] will be utilized to assess the effects of regressors/covariates such as vaccine group, visit (blood sampling timepoint), baseline or at birth GBS6 serotype-specific IgG antibody level, gender (male or female), age at vaccination (years), delivery outcome (pre-term or full-term) CCI [redacted] on the associated GBS6 serotype-specific after vaccination or after delivery IgG antibody levels. Details regarding the specific model used for maternal subjects and infant subjects are provided in Section 6.3.2.1 and Section 6.3.3.1 respectively. An unstructured covariance matrix will be used to account for intrasubject correlation. In case the model does not converge, other covariance structures (e.g. autoregressive, compound symmetry) will be explored. The baseline and after vaccination 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 that are insufficient sera (QNS), indeterminate results, or recorded as "Not Done" will be set to missing. No imputation will be done for these missing values.

CCI [redacted]

The GBS6 IgG, CCI [redacted] and OPA antibody levels above LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ or denoted as below limit of quantitation (BLQ) will be set to 0.5*LLOQ for all analysis.

[redacted]

[redacted]

5.3.2. Safety Data

Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in the Safety Rulebook Summary[6].

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 1-7' data will be considered as non-missing.

The reactogenicity data are collected through e-diary, which does not allow subjects to skip the question. Therefore, for a specific day, as long as the e-diary data is transferred for that day, all of the reactogenicity data for the subject on that day is non-missing. 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 Investigational Product

Endpoints: Maximum severity during the analysis time interval for pain at injection site, redness and swelling.

- Analysis timepoints: Days 1-7.
- Analysis population: Safety population for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: 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

6.1.1.2. Proportion of Nonpregnant Women Reporting Prompted Systemic Events Within 7 Days Following Administration of Investigational Product

Endpoints: Maximum severity during the analysis time interval for fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain.

- Analysis timepoints: Days 1-7.
- Analysis population: Safety population for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: 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

6.1.1.3. Proportion of Nonpregnant Women Reporting AEs Through 1 Month Following Administration of Investigational Product

Endpoints: Adverse events experienced by nonpregnant women (Stage 1).

- Analysis timepoints: 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: Number of subjects 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.
- Tier-2 AEs: Number of subjects 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 Investigational Product

Endpoints: MAEs and SAEs experienced by nonpregnant women (Stage 1).

- Analysis timepoints: Day 1 to 6 months 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: Number of subjects with events (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.

Figures: None

6.1.2. Primary Endpoint(s): Maternal Subjects (Stages 2 and 3)

6.1.2.1. Proportion of Sentinel-Cohort Maternal Subjects (Stage 2 only) With Clinical Laboratory Abnormalities Following Administration of 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 timepoint: Visit 2 (2 weeks after vaccination).
- Analysis population: Safety population for maternal subjects (Stage 2 only).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: n and proportion will be presented for normal and each grade (1 thru 4) for laboratory parameters (Hemoglobin, WBC, …) by vaccine group for sentinel cohort maternal subjects from Stage 2 only.

Figures: None

6.1.2.2. Proportion of Maternal Subjects Reporting Prompted Local Reactions Within 7 Days Following Administration of Investigational Product

Endpoints: Maximum severity during the analysis time interval for pain at injection site, redness and swelling.

- Analysis timepoints: Days 1-7.
- Analysis population: Safety population for maternal subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: 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 Subjects Reporting Prompted Systemic Events Within 7 Days Following Administration of Investigational Product

Endpoints: Maximum severity during the analysis time interval for fever, nausea/vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain.

- Analysis timepoints: Days 1-7.
- Analysis population: Safety population for maternal subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: 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 Subjects Reporting AEs Through 1 Month After Administration of Investigational Product

Endpoints: Adverse events experienced by maternal subjects (Stages 2 and 3).

- Analysis timepoints: Day 1 to 1 month after vaccination.
- Analysis population: Safety population for maternal subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: Number of subjects 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.
- Tier-2 AEs: Number of subjects 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 Subjects With SAEs, MAEs, and Obstetric Complications Through the 12-Month After delivery Visit

Endpoints: MAEs, SAEs and obstetric complications (prepartum, intrapartum, and postpartum) experienced by maternal subjects (Stages 2 and 3).

- Analysis timepoints: Day 1 to 12-Month after delivery visit.
- Analysis population: Safety population for maternal subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: Number of subjects with events (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.

Figures: None

6.1.2.6. Proportion of Maternal Subjects With Each Delivery Outcome and Delivery Mode

Endpoints: Mode of delivery (vaginal, cesarean section) and outcome at delivery (full-term live birth, premature live birth, stillbirth, spontaneous abortion, induced/elective abortion) for maternal subjects (Stages 2 and 3).

- Analysis timepoint: Delivery visit.
- Analysis population: Safety population for maternal subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: Number of subjects (n) and corresponding proportion for each category displayed by vaccine group.

Figures: None

6.1.3. Primary Endpoint(s): Infant Subjects (Stages 2 and 3)

6.1.3.1. Proportion of Infant Subjects With Specific Birth Outcomes

Endpoints: Infant cry immediately after delivery (yes, no), infant suckle after delivery (yes, no), newborn normal (yes, no), congenital malformation anomaly (yes, no) and other neonatal problem/abnormality (yes, no) for infant subjects (Stages 2 and 3).

- Analysis timepoint: Delivery visit.
- Analysis population: Safety population for infant subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: Number of subjects (n) and corresponding proportion for each category displayed by vaccine group.

Figures: None

6.1.3.2. Proportion of Infant Subjects With AEs From Birth to 6 Weeks of Age

Endpoints: Adverse events experienced by infant subjects (Stages 2 and 3).

- Analysis timepoints: Birth to 6 weeks of age.
- Analysis population: Safety population for infant subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: Number of subjects 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.
- Tier-2 AEs: Number of subjects 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 Subjects 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 subjects (Stages 2 and 3).

- Analysis timepoints: Birth to 12 months of age.
- Analysis population: Safety population for infant subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: Number of subjects 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.

Figures: None

6.2. Secondary Endpoint(s)

6.2.1. Secondary Endpoint(s): Nonpregnant Women (Stage 1)

6.2.1.1. GBS Serotype-Specific IgG GMCs Measured at 1 Month After Vaccination in Nonpregnant Women

Endpoints: GBS serotype-specific IgG antibody concentrations.

- Analysis timepoint: One (1) month after vaccination.
- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) populations for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: Number of subjects with valid assay data (n), GMCs and associated 2-sided 95% CI will be presented for each serotype by vaccine group.

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical reverse cumulative distribution curves (RCDCs) for 1 month after vaccination timepoint will be generated separately for each serotype by vaccine group.

6.2.1.2. GBS Serotype-Specific OPA GMTs Measured at 1 Month After Vaccination in Nonpregnant Women

Endpoints: GBS serotype-specific OPA antibody titers.

- Analysis timepoint: One (1) month after vaccination.
- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) populations for nonpregnant women (Stage 1).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: Number of subjects with valid assay data (n), GMTs and associated 2-sided 95% CI will be presented for each serotype by vaccine group.

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical reverse cumulative distribution curves (RCDCs) for 1 month after vaccination timepoint will be generated separately for each serotype by vaccine group.

6.2.2. Secondary Endpoint(s): Maternal Subjects (Stages 2 and 3)

6.2.2.1. GBS Serotype-Specific IgG GMCs Measured at 2 Weeks, 1 Month After Vaccination and at Delivery in Maternal Subjects

Endpoints: GBS serotype-specific IgG antibody concentrations.

- Analysis timepoints: Two (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 subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics and MMRM.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: Number of subjects with valid assay data (n), GMCs and associated 2-sided 95% CI will be presented for each analysis timepoint and serotype by vaccine group.
- GMCs and associated 95% CI from the MMRM analysis specified in Section 6.3.2.1.

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical reverse cumulative distribution curves (RCDCs) for 1 month after vaccination and delivery timepoints will be generated separately for each serotype by vaccine group.

6.2.2.2. GBS Serotype-Specific OPA GMTs Measured at 2 Weeks, 1 Month After Vaccination and at Delivery in Maternal Subjects

Endpoints: GBS serotype-specific OPA antibody titers.

- Analysis timepoint: Two (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 subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Secondary objective.

Reporting results:

- Raw data: Number of subjects with valid assay data (n), GMTs and associated 2-sided 95% CI will be presented for each analysis timepoint and serotype by vaccine group.

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical reverse cumulative distribution curves (RCDCs) for 1 month after vaccination and delivery timepoints will be generated separately for each serotype by vaccine group.

6.2.3. Secondary Endpoint(s): Infant Subjects (Stages 2 and 3)

6.2.3.1. GBS Serotype-Specific IgG GMCs Measured at Birth in Infant Subjects

Endpoints: GBS serotype-specific IgG antibody concentrations.

- Analysis timepoint: At birth.

- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) populations for infant subjects (Stages 2 and 3).

- Analysis methodology: Descriptive summary statistics and MMRM.

- Supporting objective: Secondary objective.

Reporting results:

- Raw data: Number of subjects with valid assay data (n), GMCs and associated 2-sided 95% CI will be presented for each 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 reverse cumulative distribution curves (RCDCs) for the at birth timepoint will be generated separately for each serotype by vaccine group.

6.2.3.2. GBS Serotype-Specific OPA GMTs Measured at Birth in Infant Subjects

Endpoints: GBS serotype-specific OPA antibody titers.

- Analysis timepoint: At birth.

- Analysis population: Evaluable immunogenicity and mITT (provided there is a sizable difference with evaluable) populations for infant subjects (Stages 2 and 3).

- Analysis methodology: Descriptive summary statistics.

- Supporting objective: Secondary objective.

Reporting results:

- Raw data: Number of subjects with valid assay data (n), GMTs and associated 2-sided 95% CI will be presented for each serotype by vaccine group.

Figures: The following figures will be based on the evaluable immunogenicity population only.

- Empirical reverse cumulative distribution curves (RCDCs) for the at birth timepoint will be generated separately for each serotype by vaccine group.

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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 as described in Section 3.4.1 (e.g. age at vaccination) will be generated by vaccine group and the total sample based on safety population.

The number and proportion of subjects with at least 1 medical history preferred term, arranged by system organ class will be tabulated for each vaccine group and the total sample. The medical history summary is based on the safety population.

Subject 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 Subjects (Stages 2 and 3)

Descriptive summary statistics for demographic characteristics, current alcohol and tobacco usage and obstetric history as described in Section 3.4.2 will be generated by vaccine group and the total sample based on safety population.

The number and proportion of subjects with at least 1 medical history preferred term, arranged by system organ class will be tabulated for each vaccine group and the total sample. The medical history summary is based on the safety population.

Subject data listings for demography and baseline characteristics data will also be generated.

6.6.1.3. Demographics and Feeding Information: Infant Subjects (Stages 2 and 3)

Descriptive summary statistics for demographic characteristics and feeding information as described in Section 3.4.3 will be generated by vaccine group and the total sample based on safety population.

Subject data listings for demography and other infant data will also be generated.

6.6.2. Study Conduct and Subject Disposition

The number and proportion of randomized subjects will be included in the subject disposition summary. In addition, subjects who completed each follow-up visit, withdrew before the follow-up visit along with the reasons for withdrawal, will be tabulated by vaccine group. The reasons for withdrawal will be those as specified in the database. Additionally, subjects who missed at least one study procedure but continued in the study for safety follow-up will be summarized. Subject disposition tables will be generated separately for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3) and infant subjects (Stages 2 and 3).

Subjects 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 (Stage 1), maternal subjects (Stages 2 and 3) and infant subjects (Stages 2 and 3).

The number and proportion of subjects randomized, vaccinated and had blood drawn within the protocol-specified time frame, outside the specified window will be tabulated by vaccine group and the total sample. These summaries will be generated separately for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3) and infant subjects (Stages 2 and 3).

The number and proportion of subjects with e-diary data not transmitted, transmitted by day (Days 1-7) and "All days" will be summarized by vaccine group and the total sample. These summaries will be generated separately for nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3).

Subject data listings of subjects who withdrew during the study will be generated. Also, data listings for subjects excluded from evaluable and mITT populations will be generated separately. These listings will be generated separately for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3) and infant subjects (Stages 2 and 3).

The protocol deviations listings will be generated separately for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3) and infant subjects (Stages 2 and 3). In addition, subjects who do not receive the vaccine as randomized will be listed separately for nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3).

6.6.3. Study Treatment Exposure

Not applicable.

6.6.4. Concomitant Medications and Non-Drug Treatments

No data on Non-Drug treatments are collected in this study.

Nonstudy vaccines and medications taken after signing the informed consent 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 (Stage 1), maternal subjects (Stages 2 and 3) and infant subjects (Stages 2 and 3).

Antipyretic medication taken prior to vaccination by nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) will be summarized separately. Additionally, antibiotic medication taken by maternal subjects (Stages 2 and 3) and infants (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 a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered 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.

Adverse events will be reported in accordance with the Pfizer reporting standards. For tier-2 and tier-3 events, the proportion of subjects 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 informed consent and prior to vaccination will be summarized separately.

Listings of subjects reporting any AE and immediate AEs will be generated.

All summaries and listings for the AEs will be generated separately for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3) and infant subjects (Stages 2 and 3). Additionally, GBS infections for infant subjects (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 subjects (Stages 2 and 3), the number and percent of subjects with individual systemic events along with the corresponding 2-sided 95% CIs will be displayed separately by vaccine group.

The number and percent of subjects with individual local reactions and any local reaction will be summarized on each of Days 1-7 separately. Two (2)-sided 95% CIs will also be displayed. A similar set of output 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 subject data listing will be provided for all reactogenicity data and a listing for subjects experiencing severe redness or swelling.

All summaries and listings for the reactogenicity data will be generated separately for nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3).

6.7.3. Laboratory Data

Descriptive summaries for laboratory abnormalities at 2-week after vaccination visit as described in Section 3.6.3 will be provided by vaccine group. Also, separate listings for subjects with abnormal laboratory results at 2-week after vaccination visit and subjects retested for abnormal laboratory results at screening or 2-week after vaccination visits will be generated. These summaries and listings will be generated only for the maternal subjects (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 (Stage 1), maternal subjects (Stages 2 and 3) and infant subjects (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 subjects (Stages 2 and 3).

7. ANALYSES TIMING

7.1. Introduction

This is a Phase 1/2, randomized, placebo-controlled, observer-blinded study. Analyses results after each analysis 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 E-DMC to occur approximately twice a year. Additional details can be found in the E-DMC charter.

An IRC will review the 1-month postvaccination safety data from Stage 1 and the 1-month safety and immunogenicity data of the various GBS6 formulations from the FIH Phase 1/2 study before progression into Stage 2. Additionally, IRC will review unblinded 14-day safety data for maternal subjects 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 subjects 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, 3 unblinded interim analyses are planned, one in each stage of the study.

The first interim analysis will be performed when 1-month postvaccination safety data from all subjects enrolled in Stage 1 are available. Stage 2 of the study will be initiated based on results from the first interim analysis as well as those from the 1-month postvaccination safety and immunogenicity data of 3 different dose levels of GBS6 formulated with or without $AlPO_4$ from the prior US FIH Phase 1/2 study (C1091001). Both the IRC and E-DMC will review all 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 6-week after delivery/birth safety and immunogenicity data from all maternal subjects and their infant subjects in Stage 2 are available. All available safety and immunogenicity data from all study participants will be included in the analysis. The primary objective of the second interim analysis is to select a dose and formulation for Stage 3. These unblinded data will be reviewed by both the IRC and E-DMC. However, the IRC will select the GBS6 final dose and formulation to take into Stage 3 and further development.

The third interim analysis will be performed when 6-week after delivery/birth safety and immunogenicity data from all maternal subjects and their infant subjects in Stage 3 are available. All available safety and immunogenicity data from all study participants will be included in the analysis. The primary objective of the third interim analysis is to support internal development decisions and potential regulatory agency interactions for the program.

No multiplicity adjustments will be applied for these assessments.

Sponsor study team members will be unblinded to vaccine assigned/received at the subject level within a stage at the time of the interim analysis. 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 after delivery/birth follow-up visit for subjects in Stage 3, a clinical study report (CSR) including all safety and immunogenicity data gathered from all subjects from each of the 3 stages will be issued. Safety and immunogenicity data from maternal subjects who receive the same vaccine dose/formulation or placebo in

Stages 2 and 3 will be combined and analyzed together. Safety and immunogenicity data from infant subjects who are born to maternal subjects receiving the same vaccine dose/formulation or placebo in Stages 2 and 3 will be combined and analyzed together.

8. REFERENCES

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9. APPENDICES

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) Amendment 2 for Study C1091002 is based on Protocol Amendment 4 dated 25-Nov-2020.

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 subjects 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 subjects 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 [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 C C I [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	

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 subjects born to women 18 to 40 years of age 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 subjects 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 subjects delivered to maternal subjects vaccinated with GBS6.

- To assess placental transfer of antibody from maternal subjects vaccinated with GBS6 to their infant subjects.

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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. Subjects in Stage 2 will be vaccinated between 27 0/7 and 35 6/7 weeks' gestation, and subjects in Stage 3 will be vaccinated between 24 0/7 and 35 6/7 weeks' gestation. A total of approximately 586 subjects (66 nonpregnant women and 520 maternal subjects 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 subjects enrolled/group) to receive placebo (saline control) or GBS6 (20 µg CPS/serotype/dose) with or without aluminum phosphate ($AlPO_4$).

Stage 1 subjects (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 subject through 14 days after vaccination) of the sentinel cohort of subjects at each dose level. Pregnant women, once consented, will be referred to as "maternal subjects." The first 42 eligible maternal subjects at each dose level will compose a sentinel cohort. Starting with the lowest dose level, maternal subjects will be randomly assigned (in a 1:1:1 ratio, 14 subjects 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 subjects are enrolled (expanded cohort).

Approximately 360 maternal subjects are planned to be enrolled into Stage 2 (see Table 2).

2.2.3. Stage 3

Approximately 160 additional maternal subjects will be enrolled in Stage 3 to receive a single dose/formulation of the selected GBS6 or placebo (saline control) in a 1:1 ratio.

Table 2. Planned Subjects: Total and Number in Each Stage and Group

Stage 1 Dose/Formulation Group[a]		Total (1:1:1)
Highest Dose[b]	GBS6 (20 µg CPS/serotype/dose) with $AlPO_4$	22
	GBS6 (20 µg CPS/serotype/dose) without $AlPO_4$	22
	Placebo (saline control)	22

Table 2. Planned Subjects: Total and Number in Each Stage and Group

Stage 2 Dose/Formulation Groups		Sentinel (1:1:1)	Expanded (1:1:1)	Total
Lowest Dose	GBS6 lowest dose with $AlPO_4$	14	26	40
	GBS6 lowest dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[c]
Middle Dose	GBS6 middle dose with $AlPO_4$	14	26	40
	GBS6 middle dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[c]
Highest Dose	GBS6 highest dose with $AlPO_4$	14	26	40
	GBS6 highest dose without $AlPO_4$	14	26	40
	Placebo (saline control)	14	26	40[c]
Stage 3 Dose/Formulation Group		**Total (1:1)**		
Selected Dose	Selected GBS6 dose/formulation	80		
	Placebo (saline control)	80		

Abbreviations: $AlPO_4$ = aluminum phosphate; CPS = capsular polysaccharide; FIH = first-in-human.

a. Stage 1 subjects (nonpregnant women) willing and eligible to participate will return to receive a booster dose of GBS6 (20 µg CPS/serotype/dose with $AlPO_4$) approximately 2 years after the primary dose of investigational product.

b. One hundred four healthy adults (males and females) 18 to 49 years of age have received this dose level (~52/formulation with/without $AlPO_4$) in the US FIH Phase 1/2 study (C1091001).

c. Approximately 120 pregnant control subjects 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 3 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 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 and booster doses of investigational product.

3.1.2. Primary Endpoints: Maternal Subjects (Stages 2 and 3)

- Proportions of sentinel-cohort maternal subjects (Stage 2 only) with clinical laboratory abnormalities following administration of investigational product at the 2-week follow-up visit.

- Proportions of maternal subjects reporting prompted local reactions within 7 days following administration of investigational product (pain at the injection site, redness, and swelling).

- Proportions of maternal subjects 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 subjects reporting AEs through 1 month after administration of investigational product.

- Proportions of maternal subjects 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 subjects with each delivery outcome and delivery mode.

3.1.3. Primary Endpoints: Infant Subjects (Stages 2 and 3)

- Proportions of infant subjects with specific birth outcomes.

- Proportions of infant subjects with AEs from birth to 6 weeks of age.

- Proportions of infant subjects 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 OPA geometric mean titers (GMTs) measured 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.
- GBS6 serotype-specific OPA GMTs measured before and 1 month, 3 months, and 6 months after a booster vaccination in nonpregnant women.

3.2.2. Secondary Endpoints: Maternal Subjects (Stages 2 and 3)

- GBS6 serotype-specific IgG GMCs measured at 2 weeks and 1 month after vaccination and at delivery in maternal subjects.
- GBS6 serotype-specific OPA GMTs measured at 2 weeks and 1 month after vaccination and at delivery in maternal subjects.

3.2.3. Secondary Endpoints: Infant Subjects (Stages 2 and 3)

- GBS6 serotype-specific IgG GMCs in infant subjects measured at birth.
- GBS6 serotype-specific OPA GMTs in infant subjects measured at birth.

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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 and systemic reactions 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 Subjects: 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 Subjects: Stage 2 Sentinel Cohort

Laboratory (hematology and chemistry) data will be collected for sentinel-cohort maternal subjects only. Data are collected during the screening visit, Visit 0 (-14 to -2 days prior to vaccination), and will be considered baseline data. For subjects with a rescreening visit, the rescreening laboratory results will be considered as the baseline data.

Infant Subjects: Stages 2 and 3

Day 1 is defined as the day of birth (Visit 1) for the infant subjects that corresponds to Visit 4 (delivery visit) for maternal subjects.

Day 1 is considered the baseline visit for the following assessments: immunogenicity, CCI [redacted] physical exam, and vital signs.

If Day 1 is not available for noninfant subjects, 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 one category is selected for race, the subject 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 one day before the subject's 19th birthday, the subject 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 of Regulatory Activities (MedDRA).

3.4.2. Demographics, Substance Use, Medical History, and Obstetric History: Maternal Subjects (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 one day before the subject's 19th birthday, the subject 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 results 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 Subjects (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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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 subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3) and will be categorized according to the current version (at the time of reporting) of MedDRA.

An immediate AE is defined as any AE that occurred within the first 30 minutes after administrations of the investigational product for nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) (see Section 7.8.2 [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 (Stage 1) subjects, from screening up to Visit 9 for maternal subjects (Stages 2 and 3), and up to Visit 7 for infant subjects (Stages 2 and 3). In addition, for subjects receiving the booster vaccination in Stage 1, MAEs will be assessed from Visit 5 up to Visit 9.

AEs of special interest for infant subjects (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 1-7 are referred to as early onset (EOD) and those that occurred during Days 8-90 are referred to as late onset (LOD), where Day 1 is the day of birth.

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AEs and SAEs will be captured and reported in accordance with Pfizer reporting standards and following the time period of collection outlined in Section 8.1.4 (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 subjects 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 subjects (Stages 2 and 3) during Days 1-7, starting on the day of vaccination [Day 1 (Visit 1)].

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 Subjects Reporting)

The subject 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 subject 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 subject 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 subject's local reaction as Grade 4, after physical examination of the subject 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 subject. If a subject 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 value is missing on a given day;

= 'Yes', if the subject reports the reaction as 'Yes' for redness or swelling **or** 'Mild', 'Moderate' or 'Severe' or 'Grade 4' for pain at the injection site on a given day;

= 'No' if the subject 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 below.

Table 3. Derived Variables for Each Local Reaction

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Day 1-7)	Subject reports the reaction as 'Yes' on any day (Day 1-7)	Subject reports the reaction as 'No' on all 7 days or as a combination of 'No' and missing on all 7 days.	Subject 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 below.

Table 4. Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
Any day (Day 1-7)	Subject reports any local reaction as 'Yes' on any day during Days 1-7	Subject 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.	Subject reports all of the local reactions as missing on all 7 days.

Grading Scale for Local Reactions

The grading of local reactions is listed below 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. Subjects 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 1-7;

= 0, if the subject reports all reactions as 'No' or a combination of missing and 'No' for all 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 in which the event is recorded in the e-diary or the date the event ends if it is unresolved during the subject 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. Subjects 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 subjects 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 1-7, prior to vaccination on Day 1, a baseline assessment of systemic events will be recorded in the e-diary for the maternal subjects (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 to be 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 subject is to document the presence or absence of remaining systemic events in the e-diary as 'Mild,' 'Moderate,' 'Severe,' or 'None'. Subjects are asked to assess the severity of each event according to Table 6 below. Study staff may also contact the subject to obtain additional information on Grade 3 events entered into the e-diary. Only an investigator is able to classify a subject's systemic event as Grade 4, after physical examination of the subject or documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the subject. If a subject 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. Subjects 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 subject reports a temperature ≥38.0°C for fever **or** 'Mild,' 'Moderate,' 'Severe,' or 'Grade 4' for the remaining events on a given day;

= 'No' if the subject reports a temperature <38.0°C for fever **or** 'None' for the remaining events on a given day.

For each systemic event, the following variables will be derived:

[redacted]

[redacted]

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 subjects (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 below in Table 7.

Table 7. Laboratory Tests

Hematology	Chemistry
Hemoglobin	BUN and creatinine
Hematocrit	AST, ALT
RBC count	Total bilirubin
Platelet count	Alkaline phosphatase
WBC count	
Total neutrophils (Abs)	
Eosinophils (Abs)	
Monocytes (Abs)	
Basophils (Abs)	
Lymphocytes (Abs)	

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = while blood cell.

The toxicity grading scale in Table 8 below for pregnant women 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

	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
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

Table 8. Hematology and Blood Chemistry Toxicity Grading Scale

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
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		
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

Table 8. Hematology and Blood Chemistry Toxicity Grading Scale

	Pregnancy Status	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4
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) and prebooster screening visit (Visit 5). 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), and the prebooster screening visit (Visit 5) and recorded in the CRF.

3.6.4.2. Physical Examination, Including Vital Signs: Maternal Subjects (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 subject'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 Subjects (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 Subjects (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 exam 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 Subjects (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, stillbirth, 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 subjects 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 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 medication taken to treat AEs from the signing of the ICD through Visit 9 will be recorded in the CRF.

3.7.2.2. Nonstudy Vaccines and Concomitant Treatments: Maternal Subjects (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 medication 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 Subjects (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 subjects will be assessed to determine if subjects 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 subjects, and their infant subjects: 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 subjects (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 subjects (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 subjects 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 after the 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 subjects who:

- Are eligible (have signed informed consent and met all inclusion/exclusion criteria) and assigned to the booster vaccination;
- Have received 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, subject 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 subjects with protocol violations before any immunogenicity analysis is carried out.

4.1.2. Per Protocol Analysis Set: Maternal Subjects (Stages 2 and 3)

The evaluable immunogenicity population will include subjects 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 at the delivery visit;
- Have at least 1 valid and determinate assay result for either the 1 month after vaccination or the delivery 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 Subjects (Stages 2 and 3)

The evaluable immunogenicity population will include subjects:

- Who are eligible (mother has signed informed consent and met all inclusion/exclusion criteria) and whose mother was randomized into the study. If mother is not eligible for the study, 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 subjects (Stages 2 and 3) will be summarized according to the vaccine group as randomized. The immunogenicity data for infant subjects (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 subjects between the mITT and evaluable immunogenicity populations. CCI [redacted]

4.2.1. Full Analysis Set: Nonpregnant Women (Stage 1)

All randomized subjects who have at least 1 valid and determinate assay result will be included in the mITT population.

4.2.2. Full Analysis Set: Maternal Subjects (Stages 2 and 3)

All randomized subjects who have at least 1 valid and determinate assay result will be included in the mITT population.

4.2.3. Full Analysis Set: Infant Subjects (Stages 2 and 3)

All infants of randomized maternal subjects 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 subjects and their infant subjects. The safety population is the analysis population for all the safety endpoints.

The safety data for nonpregnant women (Stage 1) and maternal subjects (Stage 2 and 3) will be summarized according to the vaccine group as administered. The safety data for infant subjects (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 subjects who received a primary dose of GBS6 vaccine or placebo will be included in the primary vaccination safety population.

All subjects who received a booster dose of GBS6 will be included in the booster vaccination safety population.

4.3.2. Safety Analysis Set: Maternal Subjects (Stages 2 and 3)

All subjects who received the GBS6 vaccine or placebo will be included in the safety population.

4.3.3. Safety Analysis Set: Infant Subjects (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 subjects (Stages 2 and 3) who were randomized but not vaccinated and infant subjects (Stages 2 and 3) whose mothers were randomized but not vaccinated. These subjects will not be included in the safety population for safety analyses. These subjects will not be included in the evaluable immunogenicity population, but they will be included in the mITT population for immunogenicity analyses for subjects with valid and determinant assay results. The immunogenicity results for these subjects will be reported under the vaccine group as randomized or as their mothers were randomized in the case of infant subjects.

- Vaccinated but not randomized: this group includes nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) who were vaccinated but not randomized and infant subjects (Stages 2 and 3) whose mothers were vaccinated but not randomized. These subjects 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 subjects. They will be excluded from immunogenicity analyses based on either the evaluable immunogenicity or mITT populations.

- Randomized but received incorrect vaccine: this group includes nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) who were randomized but received an incorrect vaccine and infant subjects (Stages 2 and 3) whose mothers were randomized but received an incorrect vaccine. These subjects 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 subjects 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 subjects 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 subjects. 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, the subset will only include Groups 5 through 7; Stage 2 will include all vaccine groups; Stage 3 will include 1 vaccine group chosen from Groups 1-6 and Group 7. Unless otherwise explicitly stated, all Stage 2 maternal subjects from both sentinel and expanded cohorts will be combined, by vaccine groups listed above. Similarly, all Stage 2 infant subjects from both sentinel and expanded cohorts will be combined according to their mother's vaccine group.

Both immunogenicity and safety results will be summarized separately for nonpregnant women (Stage 1), maternal subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3).

5.2.1. Analyses for Binary Data

5.2.1.1. Immunogenicity Data

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 subjects, 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 subjects reporting local reactions, systemic events (Stage 1 nonpregnant women, Stages 2 and 3 maternal subjects), AEs, SAEs, and MAEs (Stage 1 nonpregnant women, Stages 2 and 3 maternal subjects and their infants), obstetric complications, delivery outcomes, and delivery mode (Stages 2 and 3 maternal subjects), and AEs of special interest (Stages 2 and 3 infant subjects).

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 (Stage 1), maternal subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3).

5.2.2. Analyses for Continuous Data

5.2.2.1. Geometric Means

The GBS6 serotype-specific IgG, CCI [redacted], and OPA, CCI [redacted] 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 [redacted]

[redacted]

CCI [redacted]

5.2.2.3. Geometric Mean Ratios

The GBS6 serotype-specific antibody level ratios of infant to mother IgG CCI [redacted] 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 [redacted].

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical reverse cumulative distribution curves (RCDCs) will be presented graphically by plotting the proportion of subjects 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 subjects 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 and OPA titers by vaccine group at blood sampling time points from before vaccination (Day 1) to after vaccination for both nonpregnant women (Stage 1) and maternal subjects (Stages 2 and 3) and similarly for infant subjects (Stages 2 and 3) by their mother's vaccine group at blood sampling time points 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 subjects will be utilized to assess the effects of regressors/covariates, such as vaccine group (maternal vaccine group for infant subjects), 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

[redacted]

[redacted]

regarding the specific model used for maternal and infant subjects 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 intrasubject 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 [redacted]

The GBS6 IgG, CCI [redacted] and OPA antibody levels above LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ or denoted as below limit of quantitation (BLQ) will be set to 0.5×LLOQ for all analysis.

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 subjects 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 subject 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 1-7.
- 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.

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 1-7.
- 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.

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 subjects with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, SAE, immediate AE, severe AE, related AE, MAE, and AE leading to withdrawal, by vaccine group. Additionally, number of subjects 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.
- Tier 2 AEs: The number of subjects 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 and 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 to 6 months 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 subjects with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, SAE, immediate AE, severe AE, related AE, MAE, and AE leading to withdrawal, by vaccine group. Additionally, number of subjects 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, and MAEs.

Figures: None

6.1.2. Primary Endpoint(s): Maternal Subjects (Stages 2 and 3)

6.1.2.1. Proportion of Sentinel-Cohort Maternal Subjects (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 subjects (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 subjects from Stage 2 only.

Figures: None

6.1.2.2. Proportion of Maternal Subjects 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 1-7.
- Analysis population: Safety population for maternal subjects (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 Subjects 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 1-7.
- Analysis population: Safety population for maternal subjects (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 Subjects Reporting AEs Through 1 Month After Administration of the Investigational Product

Endpoints: AEs experienced by maternal subjects (Stages 2 and 3).

- Analysis time points: Day 1 to 1 month after vaccination.
- Analysis population: Safety population for maternal subjects (Stages 2 and 3).

- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of subjects with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, SAE, immediate AE, severe AE, related AE, MAE, and AE leading to withdrawal, by vaccine group. Additionally, the number of subjects 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 subjects 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 Subjects 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 subjects (Stages 2 and 3).

- Analysis time points: Day 1 to the 12-month postdelivery visit.
- Analysis population: Safety population for maternal subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of subjects with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, SAE, immediate AE, severe AE, related AE, MAE, AE leading to withdrawal, and obstetric complications by pregnancy period (prepartum, intrapartum, and postpartum) by vaccine group. Additionally, the number of subjects 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 Subjects 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 subjects (Stages 2 and 3).

- Analysis time point: Delivery visit.
- Analysis population: Safety population for maternal subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of subjects (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 Subjects (Stages 2 and 3)

6.1.3.1. Proportion of Infant Subjects With Specific Birth Outcomes

Endpoints: Gestational age (weeks), 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 still birth) for infant subjects (Stages 2 and 3).

- Analysis time point: Delivery visit.
- Analysis population: Safety population for infant subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of subjects (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 Subjects With AEs From Birth to 6 Weeks of Age

Endpoints: AEs experienced by infant subjects (Stages 2 and 3).

- Analysis time points: Birth to 6 weeks of age.
- Analysis population: Safety population for infant subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of subjects with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, SAE, severe AE, MAE, and AE leading to withdrawal, by maternal vaccine group. Additionally, the number of subjects 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 subjects 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 Subjects 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 subjects (Stages 2 and 3).

- Analysis time points: Birth to 12 months of age.
- Analysis population: Safety population for infant subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Primary safety objective.

Reporting results:

- Raw data: The number of subjects with AEs (n), proportion, and associated 2-sided exact 95% CI will be presented for any AE, SAE, severe AE, MAE, AE leading to withdrawal, and AE 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 subjects 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 subjects with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented for each serotype, by vaccine group.

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.

6.2.1.2. GBS6 Serotype-Specific OPA GMTs Measured at 1 Month After the Primary Vaccination in Nonpregnant Women

Endpoints: GBS6 serotype-specific OPA antibody titers.

- 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 subjects with valid assay data (n), GMTs, and associated 2-sided 95% CI will be presented for each serotype, by vaccine group.

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.

6.2.1.3. 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 subjects with valid assay data (n), GMCs, and associated 2-sided 95% CI will be presented for each serotype, by vaccine group.

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, by vaccine group.

6.2.1.4. GBS6 Serotype-Specific OPA GMTs Measured Before and 1 Month, 3 Months, and 6 Months After the Booster Vaccination in Nonpregnant Women

Endpoints: GBS6 serotype-specific OPA antibody titers.

- 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 subjects with valid assay data (n), GMTs, and associated 2-sided 95% CI will be presented for each serotype, by vaccine group.

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, by vaccine group.

6.2.2. Secondary Endpoint(s): Maternal Subjects (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 Subjects

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 subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics and MMRM.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of subjects 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 2 Weeks and 1 Month After Vaccination and at Delivery in Maternal Subjects

Endpoints: GBS6 serotype-specific OPA antibody titers.

- 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 subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of subjects 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 time will be generated separately for each serotype by vaccine group.

6.2.3. Secondary Endpoint(s): Infant Subjects (Stages 2 and 3)

6.2.3.1. GBS6 Serotype-Specific IgG GMCs Measured at Birth in Infant Subjects

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 subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics and MMRM.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of subjects 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 Subjects

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 subjects (Stages 2 and 3).
- Analysis methodology: Descriptive summary statistics.
- Supporting objective: Secondary objective.

Reporting results:

- Raw data: The number of subjects 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.

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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 and the total sample will be based on the safety population.

The number and proportion of subjects 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.

[redacted]

[redacted]

Subject 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 Subjects (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 subjects 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.

Subject data listings for demography and baseline characteristics data will also be generated.

6.6.1.3. Demographics and Feeding Information: Infant Subjects (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.

Subject data listings for demography and other infant data will also be generated.

6.6.2. Study Conduct and Subject 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 1-7. The denominator will be the total number of subjects who received the vaccination, and the numerator will be the total number of subjects 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 subjects who completed (transmitted) the e-diary on any day, and the denominator is the total number of subjects who received a vaccination.

2. E-diaries are completed for at least 2 days. The numerator is the number of subjects who completed (transmitted) the e-diary on any 2 days, and the denominator is the total number of subjects who received a vaccination.

3. E-diaries are completed for at least 3 days. The numerator is the number of subjects who completed (transmitted) the e-diary on any 3 days, and the denominator is the total number of subjects who received a vaccination.

4. E-diaries are completed for at least 4 days. The numerator is the number of subjects who completed (transmitted) the e-diary on any 4 days, and the denominator is the total number of subjects who received a vaccination.

5. E-diaries are completed for at least 5 days. The numerator is the number of subjects who completed (transmitted) the e-diary on any 5 days, and the denominator is the total number of subjects who received a vaccination.

6. E-diaries are completed for at least 6 days. The numerator is the number of subjects who completed (transmitted) the e-diary on any 6 days, and the denominator is the total number of subjects who received a vaccination.

7. E-diaries are completed for all 7 days. The numerator is the number of subjects who completed (transmitted) the e-diary on all 7 days, and the denominator is the total number of subjects who received a vaccination.

The number and proportion of subjects with e-diary data not transmitted, transmitted by day (Days 1-7), and transmitted all days will be summarized by vaccine group and the total sample. These summaries will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1) and maternal subjects (Stages 2 and 3).

6.6.2.2. Subject Disposition

The number and proportion of randomized subjects will be included in the subject disposition summary for nonpregnant women receiving the primary and booster vaccinations from Stage 1 and for maternal subjects from Stages 2 and 3. For infant subjects from Stages 2 and 3, number and proportion of enrolled subjects will be displayed. In addition, subjects 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 subjects. The reasons for withdrawal will be those as specified in the database. Additionally, subjects who missed at least 1 study procedure but continued in the study for the safety follow-up will be summarized. Subject disposition tables will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1), maternal subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3).

Subjects 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 subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3).

The number and proportion of subjects 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 subjects 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 subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3).

Subject data listings of subjects who withdrew during the study will be generated. Also, data listings for subjects 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 subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3).

The protocol deviations listings will be generated separately for nonpregnant women receiving the primary and booster vaccinations (Stage 1), maternal subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3). In addition, subjects 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 subjects (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 subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3).

Antipyretic medication taken prior to vaccination by nonpregnant women receiving the primary and booster vaccinations (Stage 1) and maternal subjects (Stages 2 and 3) will be summarized separately. Additionally, antibiotic medication taken by maternal subjects (Stages 2 and 3) and infant subjects (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 subjects 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 subjects from Stages 2 and 3.

Listings of subjects reporting any AE will be generated for all subjects.

Additionally, immediate AEs will be generated for nonpregnant women receiving the primary and booster vaccinations from Stage 1 and for maternal subjects 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 subjects (Stages 2 and 3), and infant subjects (Stages 2 and 3). Additionally, suspected or confirmed GBS infections for infant subjects (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 subjects (Stages 2 and 3), the number and percentage of subjects with individual systemic events along with the corresponding 2-sided 95% CIs will be displayed separately, by vaccine group.

The number and percentage of subjects with individual local reactions and any local reaction will be summarized on each of Days 1-7 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 subject data listing will be provided for all reactogenicity data and for subjects experiencing severe redness or swelling.

All summaries and listings for the reactogenicity data will be generated separately for nonpregnant women (Stage 1) and maternal subjects (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 subjects with abnormal laboratory results at 2 weeks after vaccination and subjects 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 subjects (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 subjects (Stages 2 and 3), and infant subjects (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 subjects (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 subjects 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 subjects 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 subjects 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 subjects and their infants in Stage 2 are available. Safety and immunogenicity data from all sentinel-cohort maternal subjects 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 subjects and their infants in Stage 2 are available. All available safety and immunogenicity data from all Stage 2 (maternal and infant) subjects 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 subjects and their infants in Stage 3 are available. All available safety and immunogenicity data from all Stage 3 (maternal and infant) subjects 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 subjects 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 subjects in Stage 3, a clinical study report (CSR), including all unblinded safety, immunogenicity, and CCI [redacted] data gathered from all subjects from each of the 3 stages, will be issued. Safety and immunogenicity data from subjects who receive the same vaccine, dose/formulation, or placebo in Stages 2 and 3 will be combined and analyzed together for maternal subjects and also analyzed together for their infant subjects.

8. REFERENCES

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9. APPENDICES

Table 11. Summary of Immunogenicity [redacted] Data Analyses [redacted]

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 [redacted] 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 subjects 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 subjects 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 [redacted] 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
				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

[redacted]

[redacted]

Table 11. Summary of Immunogenicity CCI Data Analyses CCI

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
			GBS6 serotype-specific OPA following primary vaccination	GMTs 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
				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
			GBS6 serotype-specific OPA following booster vaccination	GMTs CCI from before the booster vaccination 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
				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
			CCI			

[redacted]

[redacted]

Table 11. Summary of Immunogenicity CCI Data Analyses CCI

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
			CCI			

[redacted]

[redacted]

Table 11. Summary of Immunogenicity and Colonization Data Analyses (Excluding Subgroup)

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
	CCI [redacted]					
2 and 3 combined (maternal)	Evaluable immunogenicity population for maternal subjects	Blood	GBS6 serotype-specific IgG	GMCs CCI [redacted] from Day 1 to each postvaccination time point along with respective 95% CIs	Day 1, 2 weeks and 1 month after vaccination, delivery, and 6 weeks and 12 months after delivery	Continuous
				Proportion of subjects achieving a defined IgG level (eg, 1.0 µg/mL) and corresponding 95% CIs	Day 1, 2 weeks and 1 month after vaccination, delivery, and 6 weeks and 12 months after delivery	Binary
				RCDCs	1 Month after vaccination and delivery	Continuous
				Antibody response curves	Day 1, 2 weeks and 1 month after vaccination, 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), CCI [redacted] on the associated GBS6 serotype-specific postvaccination IgG antibody levels	Day 1, 2 weeks and 1 month after vaccination, delivery, and 6 weeks and 12 months after delivery	Continuous
			GBS6 serotype-specific OPA	GMTs CCI [redacted] from Day 1 to each postvaccination time point along with respective 95% CIs	Day 1, 2 weeks and 1 month after vaccination, delivery, and 6 weeks and 12 months after delivery	Continuous

Table 11. Summary of Immunogenicity CCI Data Analyses CCI

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
				RCDCs	1 Month after vaccination and delivery	Continuous
				Antibody response curves	Day 1, 2 weeks and 1 month after vaccination, delivery, and 6 weeks and 12 months after delivery	Continuous
			CCI			
			GBS6 serotype-specific IgG CCI	GMRs for CCI /IgG along with respective 95% CIs	Day 1, 1 month after vaccination, and delivery	Continuous
	CCI					
2 and 3 combined (infant)	Evaluable immunogenicity population for infant subjects	Blood	GBS6 serotype-specific IgG	GMCs 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 subjects 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 CCI [redacted] Data Analyses CCI [redacted]

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), and at-birth 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 CCI [redacted] from birth through 14 weeks of age along with respective 95% CIs	At birth and 6 weeks and 14 weeks of age	Continuous
				RCDCs	At birth	Continuous
				Antibody response curves	At birth and 6 weeks and 14 weeks of age	Continuous
			CCI [redacted]			

[redacted]

[redacted]

Table 11. Summary of Immunogenicity CCI Data Analyses CCI

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
	CCI					

[redacted]

[redacted]

Table 11. Summary of Immunogenicity CCI Data Analyses CCI

Stage(s)	Population	Sample	Outcome	Analysis	Analysis Time Points	Data Type
	CCI					
2 and 3 combined (maternal and infant pairs)	Evaluable immunogenicity population for maternal and infant pairs	Blood	Ratio of infant to maternal GBS6 serotype-specific IgG	GMRs and corresponding 95% CIs	At birth/delivery	Continuous
			CCI			

Investigating for immunological correlates of protection against invasive Group B *streptococcus* disease in infants less than 90 days of age.

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Abbreviations

CHBH	Chris Hani Baragwanath Hospital
RMPRU	Respiratory and Meningeal Pathogens Research Unit
BMH	Bheki Mlangeni Hospital
CDC	Centers for Disease Control and Prevention
CHBAH	Chris Hani Baragwanath Academic Hospital
CLSI	Clinical and Laboratory Standards Institute
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CPS	Capsular polysaccharide
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
EC	Ethics Committee
EDC	Electronic Data Capture
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EOD	Early onset disease
FDA	Food and Drug Administration
FSFV	First Subject First Visit
GBS	Group B Streptococcus/Streptococcus agalactiae
GBS-CV	Group B Streptococcus protein-polysaccharide conjugate vaccine
GBS-TCV	Group B Streptococcus Tri-valent protein-polysaccharide conjugate vaccine
GCP	Good Clinical Practice
GM	Geometric Mean
GPP	Good Pharmaco-epidemiology Practice
GSK	Glaxo Smith Kline
HREC	Human Research Ethics Committee
IAP	Intra-partum antibiotic Prophylaxis
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IRB	Institutional Review Board
LNC	Lillian Ngoyi Clinic
LOD	Late onset disease
MIA	Multiplex Immunological Assay
NHLS	National Health Laboratory Service
OPK	Opsonophagocytic killing
PCR	Polymerase Chain Reaction
RMMCH	Rahima Moosa Mother and Child Hospital
RMPRU	Respiratory and Meningeal Pathogens Research Unit
SBA	Serum bactericidal assays
SDA	Source Document Assessment