



**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 ADULTS 18 TO 49 YEARS OF AGE**

<b>Investigational Product Number:</b>	CCI [REDACTED]
<b>Investigational Product Name:</b>	Group B Streptococcus 6-Valent CCI [REDACTED] Vaccine (GBS6)
<b>United States (US) Investigational New Drug (IND) Number:</b>	17058
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**Document History**

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Protocol Amendment 3	29 August 2017	<ul style="list-style-type: none"> <li>• Added language regarding an additional voluntary blood volume collection, at Visit 4 for a subset of subjects, to support assay development. Changes were made to the following sections: Protocol Summary (study design), Schedule of Activities, Section 3, Section 6.7 and Section 7.3.</li> <li>• Clarified, in Section 4.2 exclusion criterion 14, that “postvaccination” refers to the entire 6-month study period.</li> </ul>
Protocol Amendment 2	16 May 2017	<ul style="list-style-type: none"> <li>• Removed the contraception check at Visit 6 in the Schedule of Activities and Section 6.9 to align with the 3 month duration of contraception use.</li> <li>• Revised exclusion criteria 3 to better clarify that chronic human immunodeficiency virus, hepatitis B and hepatitis C virus infections are exclusionary.</li> <li>• Removed the “for the duration of the study participation” language pertaining to method of contraception in exclusion criteria 4 and Section 4.4.1 to align with the 3 month duration of contraception use.</li> <li>• <b>CCI</b> [REDACTED]</li> <li>• Clarified the unblinded site staff member’s role in using the IRT system to assign investigational product container numbers in Section 6.3 and Section 6.4.</li> <li>• Clarified in Section 7.7 that the sentinel stopping rules are 1 to 6, not 1 to 5.</li> <li>• Removed the medical device language from</li> </ul>

Document	Version Date	Summary of Changes and Rationale
		Section 8.2.3 since this text is not applicable.
Protocol Amendment 1	08 March 2017	<ul style="list-style-type: none"> <li>• Added editorial changes throughout the document to improve clarity and to fix typographic errors.</li> <li>• CCI [REDACTED]</li> <li>• Removed “New or worsening” from joint pain and muscle pain in Table 5 (Systemic Event Grading Scale) for internal alignment of wording throughout the protocol.</li> <li>• CCI [REDACTED]</li> <li>• CCI [REDACTED]</li> <li>• CCI [REDACTED]</li> <li>• Modified wording in Section 7.5.2.3 to state that study staff must (vs may) contact subject to obtain additional information if a temperature of &gt;102°F is entered into an e-diary to make wording consistent with Section 6.10.</li> <li>• Added “The investigator determined it was not needed” to Section 6.10 to align with CRF approved template wording.</li> <li>• Rearranged the primary objective endpoints in chronological order according to collection times in the study.</li> <li>• CCI [REDACTED]</li> </ul>

Document	Version Date	Summary of Changes and Rationale
		<p>CCI [REDACTED]</p> <ul style="list-style-type: none"> <li>• CCI [REDACTED]</li> <li>• Modified immunogenicity blood draws at Visits 1 to 6 from 25 mL to 30 mL to facilitate sample collection at sites, eg, to accommodate the size of collection tubes.</li> <li>• Modified Section 6.11.1 to allow Visit 5 and Visit 6 to be performed via telephone contact for subjects staying in the study for safety follow-up procedures only.</li> <li>• Added vital sign collection to the screening visit.</li> <li>• Rearranged the stopping rules to keep the fever rules together.</li> <li>• Removed the medical device complaint reporting requirements section since this section is not applicable.</li> <li>• In Sections 5.8 and 7.7, revised unblinded physician and statistician to unblinded sponsor personnel in the stopping rule assessment.</li> </ul>
Original protocol	19 September 2016	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 capsule. All GBS serotypes have been found to cause disease, 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 neurologic sequelae in 25%, and 19% suffered severe sequelae, including cognitive delay, cerebral palsy, blindness, or hearing loss. 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). Serotypes Ia, Ib, II, III, and V are most frequently associated with GBS disease in infants. 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, leading to the potential for underreporting, and underuse of intrapartum antibiotic therapy (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, the number of cases of EOD decreased since the early 1990s when recommendations for prevention were introduced. The incidence of LOD has remained relatively unchanged through the introduction of IAP in the United States. Additionally, GBS disease in pregnant and postpartum women has not been reduced, as may be expected given the short course of administration during the intrapartum period only. In other countries where interventions are less widely used or a risk-based approach to IAP is used, such as in certain European countries, the trend in incidence rates may be unchanged or increasing slightly. Neither approach has eliminated GBS disease in infants. Even with potential underreporting, the highest rates of GBS disease are found in LMICs, where healthcare access and standards of prenatal care may vary, or the resources for significant preventive interventions are not available.

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 to date has demonstrated no unusual patterns of pregnancy complications or fetal outcomes.

CCI



The Phase 1/2, randomized, placebo-controlled, observer-blinded study described here will be the first-in-human (FIH) evaluation of the investigational GBS6. CCI



## **Primary Objective and Endpoints**

### **Primary Objective**

- To describe the safety and tolerability of various formulations of GBS6 at 3 dose levels in healthy adults 18 to 49 years of age.

### **Primary Endpoints**

- The proportion of sentinel-cohort subjects with clinical laboratory abnormalities following investigational product administration at the 1-week follow-up visit.

- The proportion of subjects reporting prompted local reactions within 14 days following investigational product administration (redness, swelling, and pain at the injection site).
- The proportion of subjects reporting prompted systemic events within 14 days following investigational product administration (fever, nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain).
- The proportion of subjects reporting adverse events (AEs) within 1 month following investigational product administration.
- The proportion of subjects reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) within 6 months following investigational product administration.

### 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 adults aged 18 to 49 years.

Approximately 363 healthy adults aged 18 to 49 years of age will be randomized to receive a single dose of 1 of 3 dose levels of GBS6, formulated with or without AlPO<sub>4</sub>, or placebo (saline control). This study will utilize a sentinel-cohort design CCI [REDACTED]

Blood will be collected at screening and at the 1-week postvaccination follow-up visit in all subjects enrolled in each sentinel cohort for hematology and chemistry assessments. CCI [REDACTED]

[REDACTED]. For all subjects, blood will also be collected on the day of investigational product administration prior to study vaccination and 1 week, 2 weeks, 1 month, 3 months, and 6 months after vaccination for immunogenicity assessment. Local reactions and systemic events will be collected for 14 days after vaccination. AEs will be assessed up to 1 month after vaccination. SAEs and MAEs will be assessed through 6 months after vaccination. In addition, AEs occurring up to 48 hours after the Visit 5 and Visit 6 blood draws that are related to study procedures will be collected.

CCI [REDACTED]

CCI [REDACTED]

### **Investigational Products**

The investigational products are GBS6, composed of CPS of serotypes Ia, Ib, II, III, IV, and V, individually CCI [REDACTED] at dose levels of 5, 10, or 20 µg CPS/serotype/dose, formulated with or without AlPO<sub>4</sub>, and placebo (saline control). Subjects will receive 1 dose of either GBS6, formulated with or without AlPO<sub>4</sub>, or placebo (saline control) at Visit 1 administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm.

### **Statistical Methods**

This is a Phase 1/2 FIH study to assess the safety, tolerability, and immunogenicity of GBS6 administered with or without AlPO<sub>4</sub>, and the study sample sizes are not based on statistical considerations.

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

At the completion of the 1-month follow-up blood sampling and assays, an analysis of available immunogenicity and safety results will be conducted. No multiplicity adjustments will be applied for these analyses.

### 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.

Visit Number	0	1		2	3	4	5	6
Visit Description	Screening Sentinel Cohorts Only <sup>a</sup>	Vaccination Sentinel Cohorts	Vaccination Expanded Cohorts	1-Week Follow-up Visit	2-Week Follow-up Visit	1-Month Follow-up Visit	3-Month Follow-up Visit	6-Month Follow-up Visit
Visit Window (Days) <sup>b</sup>	Day -14 to -2 Prior to Day 1	Day 1	Day 1	7-10 Days After Visit 1	14-17 Days After Visit 1	28-38 Days After Visit 1	80-100 Days After Visit 1	160-200 Days After Visit 1
Informed consent	X		X					
Demography	X		X					
Medical history	X		X					
Vital signs	X	X	X					
Physical examination	X		X					
Urine pregnancy test		X	X					
Record nonstudy vaccine information	X	X	X	X	X	X	X	X
Record medication information	X	X	X	X	X	X		
Review inclusion and exclusion criteria	X		X					
Blood draw for hematology and chemistry assessments <sup>c</sup>	X (~10 mL)			X (~10 mL)				
Prevaccination oral temperature		X	X					
Review laboratory results <sup>d</sup>		X			X			
Contraception check <sup>e</sup>		X	X	X	X	X	X	
Review continued eligibility		X		X	X	X	X	X
Review temporary delay criteria		X	X	X	X	X	X	X
Assign single subject identifier	X		X					
Assign subject randomization and container number		X	X					

Visit Number	0	1		2	3	4	5	6
Visit Description	Screening Sentinel Cohorts Only <sup>a</sup>	Vaccination Sentinel Cohorts	Vaccination Expanded Cohorts	1-Week Follow-up Visit	2-Week Follow-up Visit	1-Month Follow-up Visit	3-Month Follow-up Visit	6-Month Follow-up Visit
Visit Window (Days) <sup>b</sup>	Day -14 to -2 Prior to Day 1	Day 1	Day 1	7-10 Days After Visit 1	14-17 Days After Visit 1	28-38 Days After Visit 1	80-100 Days After Visit 1	160-200 Days After Visit 1
Blood draw for immunogenicity assessment <sup>c</sup>		X (~30 mL)	X (~30 mL)	X (~30 mL)	X (~30 mL)	X (~30 mL or ~50 mL)	X (~30 mL)	X (~30 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 <sup>f</sup>		X	X					
Review and/or collect e-diary <sup>g</sup>		X	X	X	X			
<b>CCI</b>								
Record adverse events	X	X	X	X	X	X	X <sup>i</sup>	X <sup>i</sup>
Record medically attended adverse events and serious adverse events	X	X	X	X	X	X	X	X

Abbreviations: e-diary = electronic diary; GBS = group B streptococcus.

- a. If abnormal laboratory values (as defined in Screening, [Section 6.1](#), and in [Section 7.5.3](#)) are reported at Visit 0 and the investigator believes the results to be erroneous, the abnormal laboratory parameters may be retested. See [Section 6.2](#) for further details.
- b. Day relative to start of study vaccination (Day 1).
- c. All blood volumes are approximate. Blood draw for hematology and chemistry laboratory assessments will only be performed in subjects from the sentinel cohorts. At Visit 4, an optional immunogenicity blood draw of approximately 50 mL will be collected from a subset of subjects who provide supplemental consent.
- d. Applies to sentinel-cohort subjects only.
- e. The contraception check is an opportunity to confirm that contraception is used consistently and correctly.
- f. Subjects will record reactogenicity events in an e-diary each evening for 14 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 14 following vaccination to determine if an unscheduled visit is required (see [Section 6.10](#)).
- g. Designated site staff will review e-diary data online following vaccination to evaluate subject compliance and as part of the ongoing safety review.
- h. **CCI**
- 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.



## 1. INTRODUCTION

### 1.1. Indication

Group B streptococcus 6-valent CCI [REDACTED] 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 capsule. All GBS serotypes have been found to cause disease, but there is variability in their global prevalence and virulence.<sup>1,2</sup> 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.<sup>3,4,5,6</sup> 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.<sup>7</sup> Among infants, GBS may cause serious disease, including sepsis, meningitis, and pneumonia; less common manifestations include skin and soft tissue, bone, and joint infections.<sup>8</sup> 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).<sup>9</sup> Bacteremia without a focus, cellulitis, bone and joint infections, and urinary tract infections are common disease manifestation of GBS infection in older nonpregnant adults.<sup>5,10,11</sup>

#### 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.<sup>4,12,13</sup> 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.<sup>14</sup> 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).<sup>13,15,16,17</sup> Of infants surviving GBS meningitis, one study found mild to moderate neurologic sequelae in 25%, and 19% suffered severe sequelae, including cognitive delay, cerebral palsy, blindness, or hearing loss.<sup>18</sup> Five serotypes (Ia, Ib, II, III, V) are most frequently associated with GBS disease in infants. Another serotype (IV) shows a trend of increased prevalence in certain regions.<sup>4</sup> 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.<sup>6</sup> The most common clinical syndrome in EOD is sepsis/bacteremia without a focus, whereas LOD is more likely to be associated with a focus,<sup>3,6,15</sup> with meningitis being more common in LOD (21%-59% of LOD cases).<sup>3,6,15</sup> Additionally, serotype III appears to be a relatively

prominent cause of LOD (causing 51%-67% of LOD),<sup>3,6,15</sup> 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 therapy (IAP) to prevent GBS disease.<sup>4</sup> 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 0.25 cases/1000 live births in 2014.<sup>19,20</sup> 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.<sup>21</sup> The incidence was 0.28 cases/1000 live births in 2014.<sup>20</sup> Despite significant declines in the incidence of pediatric bacterial meningitis, the incidence among infants under 2 months of age, which is the group at greatest risk for bacterial meningitis, did not decrease.<sup>21</sup> GBS disease in pregnant and postpartum women does not appear to have been reduced through the introduction of IAP in the United States,<sup>14</sup> as may be expected given the short course of administration during the intrapartum period only. 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.<sup>6,22</sup> 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,<sup>15</sup> where healthcare access and standards of prenatal care may vary, or the resources for significant preventive interventions are not available.

### **1.2.3. GBS Disease in Nonpregnant Adults**

Adults ≥65 years of age are at increased risk for GBS disease, as are adults of all ages with associated comorbid conditions such as diabetes mellitus, cancer, heart failure, and neurologic and urologic conditions.<sup>3,5,6,23,24</sup> According to the CDC Active Bacterial Core surveillance (ABCs) system, the annual US incidence of invasive GBS in 2014 was 21.1 cases/100,000 in adults 65 to 74 years of age, 33.1/100,000 in adults 75 to 84 years of age, and 41.8/100,000 in adults ≥85 years of age.<sup>20</sup> The distribution of serotypes causing the bulk of invasive disease in older adults overlaps with the serotypes causing GBS disease in infants. Serotype V, however, is more prominent in adults than infants, and serotype IV is also emerging.<sup>5,6,24,25</sup>

## 1.2.4. Rationale for Development of GBS6

### 1.2.4.1. 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.<sup>26,27</sup> 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.<sup>27</sup> 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.<sup>28</sup> 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.<sup>29</sup> Safety surveillance conducted to date has demonstrated no unusual patterns of pregnancy complications or fetal outcomes.<sup>30</sup> 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, these vaccines have demonstrated an acceptable safety profile with single and repeat dosing.<sup>31,32</sup>

### 1.2.4.2. 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.<sup>33</sup> The efficiency of antibody transfer depends on placental integrity, maternal total IgG, gestational age at delivery, and IgG subclass (IgG1 subclass is most efficiently transferred).<sup>27</sup> 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.<sup>34</sup> 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.<sup>35,36,37,38</sup> 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 CCI 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.

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### 1.2.6. Study Rationale

This Phase 1/2, randomized, placebo-controlled, observer-blinded study will be the first-in-human (FIH) evaluation of the investigational GBS6. CCI

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## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Primary Objective and Endpoints

#### 2.1.1. Primary Objective

- To describe the safety and tolerability of various formulations of GBS6 at 3 dose levels in healthy adults 18 to 49 years of age.

#### 2.1.2. Primary Endpoints

The endpoints for the primary objective are listed below, in chronological order according to time of collection in the study:

- The proportion of sentinel-cohort subjects with clinical laboratory abnormalities following investigational product administration at the 1-week follow-up visit.
- The proportion of subjects reporting prompted local reactions within 14 days following investigational product administration (redness, swelling, and pain at the injection site).
- The proportion of subjects reporting prompted systemic events within 14 days following investigational product administration (fever, nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain).
- The proportion of subjects reporting adverse events (AEs) within 1 month following investigational product administration.
- The proportion of subjects reporting medically attended adverse events (MAEs) and serious adverse events (SAEs) within 6 months following investigational product administration.



initiated in parallel and each site is only allowed to enroll subjects into 1 cohort at a time. Enrollment will proceed this way in a staggered fashion throughout the study (see [Table 1](#) below for a graphic description of the enrollment/escalation plan).

Blood will be collected at screening and at the 1-week postvaccination follow-up visit in all subjects enrolled in each sentinel cohort for hematology and chemistry assessments. CCI

For all subjects, blood will also be collected on the day of investigational product administration prior to study vaccination and 1 week, 2 weeks, 1 month, 3 months, and 6 months after vaccination for immunogenicity assessment. Local reactions and systemic events will be collected for 14 days after vaccination. AEs will be assessed up to 1 month after vaccination. SAEs and MAEs will be assessed through 6 months after vaccination. In addition, AEs occurring up to 48 hours after the Visit 5 and Visit 6 blood draws that are related to study procedures will be collected.

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**Table 1. Enrollment and Dose Escalation Design**

Dose Escalation	Enrollment Strategy						
<b>Lowest Dose Cohort</b> GBS6: 5 µg <sup>a</sup> /AlPO <sub>4</sub> GBS6: 5 µg <sup>a</sup> /no AlPO <sub>4</sub> Placebo (saline control)	Enroll sentinel cohort <sup>b</sup> (n=40)	Review 14-day safety data CCI	Complete enrollment of expanded cohort <sup>d</sup> (n=81)				
<b>Middle Dose Cohort</b> GBS6: 10 µg <sup>a</sup> /AlPO <sub>4</sub> GBS6: 10 µg <sup>a</sup> /no AlPO <sub>4</sub> Placebo (saline control)			Enroll sentinel cohort (n=40)	Review 14-day safety data CCI	Complete enrollment of expanded cohort (n=81)		
<b>Highest Dose Cohort</b> GBS6: 20 µg <sup>a</sup> /AlPO <sub>4</sub> GBS6: 20 µg <sup>a</sup> /no AlPO <sub>4</sub> Placebo (saline control)					Enroll sentinel cohort (n=40)	Review 14-day safety data CCI	Complete enrollment of expanded cohort (n=81)

Abbreviations: AlPO<sub>4</sub> = aluminum phosphate; CPS = capsular polysaccharide; CCI



**3.1. Duration of Subject Participation**

Each subject will participate in the study for approximately 6 months.

**3.2. Duration of Study**

The study duration will be approximately 14 months.

**3.3. Number of Subjects**

Approximately 363 subjects will be enrolled, 52 at each dose level/formulation and 51 in the placebo group. An allocation target will not be set by sex; however, the intention is for sites to enroll at least 50% women within each dose level group. If there is a predominance of one sex enrolled, the sponsor may give direction to sites about sex-based enrollment. Refer to [Table 2](#) for a detailed description of the number of subjects per group. Subjects who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.



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

Dose Level/Formulation Groups		Approximate Number of Subjects	
		CCI	TOTAL
<b>Lowest Dose</b>	GBS6 lowest dose (5 µg <sup>c</sup> ) with AlPO <sub>4</sub>		52
	GBS6 lowest dose (5 µg <sup>c</sup> ) without AlPO <sub>4</sub>		52
	Placebo (saline control)		17
<b>TOTAL</b>			121
<b>Middle Dose</b>	GBS6 middle dose (10 µg <sup>c</sup> ) with AlPO <sub>4</sub>		52
	GBS6 middle dose (10 µg <sup>c</sup> ) without AlPO <sub>4</sub>		52
	Placebo (saline control)		17
<b>TOTAL</b>			121
<b>Highest Dose</b>	GBS6 highest dose (20 µg <sup>c</sup> ) with AlPO <sub>4</sub>		52
	GBS6 highest dose (20 µg <sup>c</sup> ) without AlPO <sub>4</sub>		52
	Placebo (saline control)		17
<b>TOTAL</b>			121
<b>Study TOTAL</b>			363

Abbreviations: AlPO<sub>4</sub> = aluminum phosphate; CPS = capsular polysaccharide.

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#### 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

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 electronic diary (e-diary) from Day 1 to Day 14 following administration of investigational product.

3. Healthy adults (male and female) 18 to 49 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) for all female subjects who are of childbearing potential.

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.

#### **4.2. Exclusion Criteria**

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) within 28 days prior to study entry (Visit 0 for subjects in sentinel cohorts, Visit 1 for subjects in expanded cohorts) and/or during study participation. Participation in purely observational studies is acceptable.
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. Chronic medical conditions include human immunodeficiency virus (HIV), chronic hepatitis B virus (HBV) infection (HBV surface antigen positive), and/or hepatitis C virus infection.

4. Male subjects and female 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 the last dose of investigational product.
5. **For sentinel-cohort subjects only**, laboratory test results at the screening visit outside of the normal reference range. Refer to [Section 6.1](#) for additional guidance if abnormal laboratory test results are reported.
6. 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 CCI.
7. History of microbiologically proven invasive disease caused by group B streptococcus (*S agalactiae*).
8. Immunocompromised subjects with known or suspected immunodeficiency.
9. 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 6-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.
10. Other severe acute or chronic medical or psychiatric condition 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.
11. Bleeding diathesis or condition associated with prolonged bleeding that would in the opinion of the investigator contraindicate intramuscular injection.

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14. Receipt or planned receipt of blood/plasma products or immunoglobulin, from 60 days before investigational product administration through the 6-month postvaccination blood draw.

### **4.3. Temporary Delay Criteria**

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

#### **4.3.1. Criteria for Temporarily Delaying Vaccine Administration**

- Current febrile illness (body temperature  $\geq 100.4^{\circ}\text{F}$  [ $\geq 38^{\circ}\text{C}$ ]) 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.

#### **4.3.2. Criteria for Temporarily Delaying Blood Draw**

The following condition does not apply to the blood draw for hematology and chemistry assessments performed at the screening visit (and rescreening visits).

- Receipt of antibiotic therapy within 72 hours before blood draw.

### **4.4. Lifestyle Requirements**

#### **4.4.1. Contraception**

All male subjects and female subjects who are of childbearing potential and are sexually active with one 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 the last dose 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.

The following highly effective methods of contraception that are acceptable for use in this study include:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject or male subject's female partner 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 (at least 1 month). Please note: All female subjects using any form of hormonal contraception other than an implanted form must also agree to use an additional method of contraception such as condoms with spermicide.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
4. For male subjects, condoms WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository).
5. Male sterilization with absence of sperm in the postvasectomy ejaculate.

#### **4.5. 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<sub>4</sub>) and placebo (saline control). Subjects will receive 1 dose of either GBS6, with or without AlPO<sub>4</sub>, or placebo (saline control) at Visit 1 administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm. See Table 2 for more information on the investigational product dose-level/formulation groups.

### 5.1. Subject Compliance

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

### 5.2. 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.

#### 5.2.1. Dosage Form(s) and Packaging

GBS6 is composed of serotypes Ia, Ib, II, III, IV, and V CPS individually conjugated to the

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There are 3 dose levels (5, 10, or 20 µg CPS/serotype/CCI each formulated either with AlPO<sub>4</sub>, CCI, or without AlPO<sub>4</sub>. See Table 3 for further details.

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### 5.2.2. 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, CCI



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.

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### 5.3. Allocation to Investigational Product

Allocation of subjects to investigational product groups will be performed 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.

#### 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).

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.

GBS6 or placebo (saline control) should be administered intramuscularly by injecting 0.5 mL into the deltoid muscle, CCI

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#### 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  $+2^{\circ}C$  to  $+8^{\circ}C$  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  $+2^{\circ}C$  to  $+8^{\circ}C$  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.

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

## **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**

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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**

Sponsor study team members will remain blinded to vaccine assigned/received at the subject level, following the principles outlined in ICH E9 guideline on Statistical Principles for Clinical Trials, Section 2.3.1,<sup>56</sup> until the analysis of all available safety and immunogenicity data 1 month after vaccination. In an event that unblinded results need to be submitted for regulatory communications prior to study team unblinding at the planned analysis, 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**

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

### **5.10.2. Permitted Nonstudy Vaccines and Medications During the Study**

- Licensed influenza vaccine may be given during the study starting 15 days after investigational product administration. If medically necessary (eg, pandemic), influenza vaccine may be given at any time.
- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration is permitted during 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.

### **5.10.3. Recording Nonstudy Vaccinations and Concomitant Medications**

The name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD to Visit 6 will be collected and recorded in the CRF.

Any medications taken from the signing of the ICD through Visit 4 will be recorded in the CRF. Additionally, any medication taken to treat AEs (per [Section 8.1.4](#)) from the signing of the ICD through Visit 6 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. Visit 0 – Screening for Sentinel-Cohort Subjects (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.

In the 14-day screening period, retesting of the clinical laboratory parameters will be allowed at the discretion of the investigator if abnormal test results are observed and 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 abnormal laboratory parameters.

If the subject is found ineligible for the study on the basis of hematology and/or blood chemistry 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 (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 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, sitting blood pressure and pulse rate, respiratory rate, and temperature (oral).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met, [Section 4](#).
- Obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments. Subjects with abnormal laboratory results (see below and [Section 7.5.3](#)) will not be eligible for randomization. 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.
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Record AEs as described in [Section 7.8](#) and [Section 8](#).
- Complete the source documents.
- The investigator or an authorized designee completes the CRF.

## **6.2. Visit 0 – Rescreening Visit for Sentinel-Cohort Subjects (Days -14 to -2 Prior to Vaccination), If Applicable**

If abnormal 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, [Section 4](#).
- Obtain a blood sample (approximately 10 mL) for analysis of hematology and blood chemistries, [Section 7.5.3](#). Retest only abnormal laboratory parameters from Visit 0.
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Record AEs as described in [Section 7.8](#) and [Section 8](#).
- Complete the source documents.
- 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.

### **6.3. Visit 1 – Vaccination (Day 1) for Sentinel-Cohort Subjects**

- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in [Section 6.11](#), and meets none of the temporary delay criteria as described in [Section 4.3](#).
- Review laboratory results.
- Prior to vaccination, measure vital signs, including weight, height, sitting blood pressure and pulse rate, respiratory rate, and temperature (oral).
- Prior to vaccination, perform a urine pregnancy test for female subjects of childbearing potential.
- Prior to vaccination, collect a blood sample of approximately 30 mL for immunogenicity assessments.
- CCI [REDACTED]
- CCI [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 system to assign the investigational product container number, 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 14, with Day 1 being the day of vaccination.
- Ask the subject to contact the site staff or investigator immediately if he or she is prompted by the e-diary from Day 1 to Day 14 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring  $\geq 21$  measuring device units [ $\geq 10.5$  cm], etc). 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.
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Record AEs as described in [Section 7.8](#) and [Section 8](#).
- Complete the subject's source documents.
- The investigator or an authorized designee completes the CRF and an unblinded site staff member updates the investigational product accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate subject compliance and as part of the ongoing safety review.

#### **6.4. Visit 1 – Vaccination (Day 1) for Expanded-Cohort Subjects**

- Obtain written informed consent before performing any study-specific procedures.
- Assign 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.
- Ensure and document that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- Prior to vaccination, measure vital signs, including weight, height, sitting blood pressure and pulse rate, respiratory rate, and temperature (oral).
- Prior to vaccination, perform a urine pregnancy test for female subjects of childbearing potential.
- Prior to vaccination, collect a blood sample of approximately 30 mL for immunogenicity assessments.
- CCI [REDACTED]
- CCI [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 system to assign the investigational product container number, 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 14, with Day 1 being the day of vaccination.
- Ask the subject to contact the site staff or investigator immediately if he or she is prompted by the e-diary from Day 1 to Day 14 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring  $\geq 21$  measuring device units [ $\geq 10.5$  cm], etc). 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.
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Record AEs as described in [Section 7.8](#) and [Section 8](#).
- Complete the subject's source documents.
- The investigator or an authorized designee completes the CRF and unblinded site staff member updates the investigational product accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate subject compliance and as part of the ongoing safety review.

#### **6.5. Visit 2 – 1-Week Follow-up Visit (7-10 Days After Visit 1) for All Subjects**

- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in [Section 6.11](#), and meets none of the blood draw temporary delay criteria as described in [Section 4.3](#).
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 30 mL for immunogenicity assessments.
- **For sentinel-cohort subjects only**, obtain a blood sample (approximately 10 mL) for hematology and blood chemistry assessments.
- Remind the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination.
- Ask the subject to contact the site staff or investigator immediately if he or she is prompted by the e-diary from Day 1 to Day 14 following vaccination to determine if an unscheduled visit is required (eg, redness or swelling at the injection site measuring



≥21 measuring device units [≥10.5 cm], etc). 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.
- The investigator or appropriately qualified designee reviews the e-diary data online to evaluate subject compliance and as part of the ongoing safety review.
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Record AEs as described in [Section 7.8](#) and [Section 8](#).
- Complete the subject's source documents.
- The investigator or an authorized designee completes the CRF.

#### **6.6. Visit 3 – 2-Week Follow-up Visit (14-17 Days After Visit 1) for All Cohort Subjects**

- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in [Section 6.11](#), and meets none of the blood draw temporary delay criteria as described in [Section 4.3](#).
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 30 mL for immunogenicity assessments.
- **For sentinel-cohort subjects only**, review laboratory results from the 1-week follow-up visit.
- 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.
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Record AEs as described in [Section 7.8](#) and [Section 8](#).
- Complete the subject's source documents.
- The investigator or an authorized designee completes the CRF.

#### **6.7. Visit 4 – 1-Month Follow-up Visit (28-38 Days After Visit 1) for All Cohort Subjects**

- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in [Section 6.11](#), and meets none of the blood draw temporary delay criteria as described in [Section 4.3](#).

- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 30 mL for immunogenicity assessments. Alternatively, for subjects who have consented to participate in the subset, collect approximately 50 mL of blood.
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Record AEs as described in [Section 7.8](#) and [Section 8](#).
- Complete the subject's source documents.
- The investigator or an authorized designee completes the CRF.

#### **6.8. Visit 5 – 3-Month Follow-up Visit (80-100 Days After Visit 1) for All Cohort Subjects**

- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in [Section 6.11](#), and meets none of the blood draw temporary delay criteria as described in [Section 4.3](#).
- Verify understanding of and compliance with protocol requirements for contraception.
- Collect a blood sample of approximately 30 mL for immunogenicity assessments.
- Record nonstudy vaccinations as described in [Section 5.10.3](#).
- Record AEs as described in [Section 7.8](#) and [Section 8](#).
- Complete the subject's source documents.
- The investigator or an authorized designee completes the CRF.

#### **6.9. Visit 6 – 6-Month Follow-up Visit (160-200 Days After Visit 1) for All Cohort Subjects**

- Ensure that the subject continues to be eligible for the study, meets none of the subject withdrawal criteria as described in [Section 6.11](#), and meets none of the blood draw temporary delay criteria as described in [Section 4.3](#).
- Collect a blood sample of approximately 30 mL for immunogenicity assessments.
- Record nonstudy vaccinations as described in [Section 5.10.3](#).
- Record AEs as described in [Section 7.8](#) and [Section 8](#).
- Complete the subject's source documents.

- The investigator or an authorized designee completes the CRF.

#### **6.10. Unscheduled Visits**

If the subject reports redness or swelling at the injection site measuring  $\geq 21$  measuring device units ( $\geq 10.5$  cm), fever  $\geq 102.1^{\circ}\text{F}$  ( $\geq 39.0^{\circ}\text{C}$ ), or severe injection site pain, nausea/vomiting, diarrhea, headache, fatigue, muscle pain, or joint pain, a telephone contact must occur as soon as possible between the 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, or
- The reaction is no longer present at the time of the telephone contact, or
- 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 (Visit 2, 3, and/or 4).

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 14 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.

### **6.11. 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 CCI, the subject may be considered for withdrawal.

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, 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.

#### **6.11.1. Withdrawal of Consent**

After investigational product administration at Visit 1, subjects who request to discontinue further study procedures (eg, blood draws) at upcoming visits, ie, Visits 2 to 6, will be asked to remain in the study for protocol-specified safety follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her. It is permissible that Visit 5 and Visit 6 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.

#### **6.11.2. 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 after a minimum of 2 documented phone calls, faxes, or emails as well as lack of response by the subject 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, [Section 8.1.3](#)) 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. All attempts to contact the subject 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**

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 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

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

## 7.3. Immunogenicity

Blood samples (approximately 30 mL/visit) for immunogenicity assessments will be collected from all subjects prior to vaccination (Day 1) and at 1 week, 2 weeks, 1 month, 3 months, and 6 months after vaccination. Sample collection, processing, storage, and shipping information can be found in the CCI [REDACTED].

The total volume of blood collected from each subject for immunogenicity will be approximately 180 mL (~30 mL/visit), or up to approximately 200 mL for those subjects who consent to a larger blood draw (~50 mL) at Visit 4. Sera will be used for immunogenicity assessments and assay development purposes.

CCI [REDACTED]

CCI [REDACTED]

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.

CCI

CCI

## 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 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 14 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, fever, and antipyretics/pain medication used to treat symptoms, each evening for 14 days following vaccination (Day 1 through Day 14, where Day 1 is the day of vaccination) on a system that uses a personal digital assistant (PDA) or other technology. This system, hereafter referred to as the 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 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 by Visit 4.

### **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.<sup>57</sup>

#### **7.5.2.1. Local Reactions**

From Day 1 to Day 14, where Day 1 is the day of vaccination, subjects will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21+), and 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**

	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)<sup>a</sup></b>	<b>Grade 4<sup>b</sup></b>
<b>Pain at injection site</b>	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 <sup>c</sup>	Emergency room visit or hospitalization
<b>Erythema/ Redness</b>	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
<b>Induration/ Swelling</b>	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

- Subjects experiencing ≥ Grade 3 local reactions are to be seen by the study site.
- 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.
- 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

From Day 1 to Day 14, where Day 1 is the day of vaccination, subjects will be asked to assess nausea/vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the 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, muscle pain, or joint pain) within 14 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**

	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)<sup>a</sup></b>	<b>Grade 4<sup>b</sup></b>
<b>Nausea/Vomiting</b>	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
<b>Diarrhea</b>	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
<b>Headache</b>	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization
<b>Fatigue/Tiredness</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization
<b>Muscle pain</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization
<b>Joint pain</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization

Abbreviation: IV = intravenous.

- Subjects experiencing ≥ Grade 3 systemic events are to be seen by the study site.
- 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.
- 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 14 days following vaccination (Days 1 to 14, where Day 1 is the day of vaccination) and at any time during the 14 days that fever is suspected. Fever is defined as an oral temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 14, temperature will be collected daily until fever has resolved (1 day of temperature less than 100.4°F [38.0°C] in order to collect a stop date in the CRF). A 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 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.

The FDA toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials will be adapted for use in grading laboratory test abnormalities. CCI

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 14, 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.

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## **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 subjects enrolled in sentinel cohorts, from Visit 1 for subjects enrolled in expanded cohorts, and up to Visit 6 (6-month follow-up visit) after vaccination with the investigational product.

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

#### 7.8.4. 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

#### 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 or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), <b>except occupational exposure</b>	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

Abbreviation: CT = clinical trial.

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](#), below). 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 14 days in the sentinel and expanded cohorts or SAE occurring within 30 days after vaccination. Additional information regarding such events and the reporting requirements can be found in the CCI

#### **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. In addition, each study subject 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 MAEs/SAEs (“active collection period”) for each 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 the screening visit, and from Visit 1 to Visit 4. Between Visit 4 and Visit 6, only MAEs and SAEs will be reported. In addition, AEs occurring up to 48 hours after the Visit 5 and Visit 6 blood draws that are related to study procedures must be reported.

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.

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

##### **8.1.4.1. 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.

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.

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.

##### **8.1.4.2. Recording Nonserious AEs and SAEs on the CRF**

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

#### **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;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- 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**

A serious adverse event 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. 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

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

### 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 ( $\times$  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 subjects enrolled in expanded cohorts in this study. 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 ( $>2 \times$  ULN) by several days or weeks. The increase in Tbili typically occurs while AST/ALT is/are still elevated above  $3 \times$  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  $>3 \times \text{ULN}$  AND a Tbili value  $>2 \times \text{ULN}$  with no evidence of hemolysis and an alkaline phosphatase value  $<2 \times \text{ULN}$  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  $>3 \times \text{ULN}$ ; or  $>8 \times \text{ULN}$  (whichever is smaller).
  - Preexisting values of Tbili above the normal range: Tbili level increased from baseline value by an amount of at least  $1 \times \text{ULN}$  **or** if the value reaches  $>3 \times \text{ULN}$  (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**

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

##### **8.4.3.1. Exposure During Pregnancy**

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 or subject's partner 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 infants 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**

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

#### **8.4.3.3. 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.

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

Abbreviations: CRF = case report form; CT = clinical trial.

##### **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 further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

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

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### 9.2. Immunogenicity Analysis

For the immunogenicity analyses, 2 analysis populations will be defined: evaluable immunogenicity and modified intent-to-treat (mITT) populations. To be included in the evaluable immunogenicity population, in general the 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. The evaluable immunogenicity

population will be considered the primary population. To be included in the mITT population, a subject must have at least 1 valid and determinate assay result related to the proposed analysis.

The immunogenicity data will be summarized according to the vaccine as received for the evaluable immunogenicity population and as randomized for the mITT population.

Immunogenicity endpoints are secondary or CCI in the study as listed in [Section 2.2](#) and [Section 2.3](#). Descriptive summary statistics will be provided for all immunogenicity endpoints. No formal comparison between dose groups will be made.

Descriptive evaluations include serotype-specific IgG GMCs and CCI

GBS 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.

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

### 9.3. Safety Analysis

All subjects receiving a dose of GBS vaccine or placebo will be included in the safety population. For the safety analyses, subjects will be analyzed according to the investigational product received.

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 are descriptive evaluations of local reactions, systemic events, AEs, MAEs, SAEs, and laboratory abnormalities. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).

Descriptive summary statistics (eg, counts and percentages) will be provided for AEs, e-diary events collected, and laboratory abnormalities, with 2-sided 95% exact CIs as appropriate.

#### **9.4. Analysis Timing**

At the completion of the 1-month follow-up blood sampling and assays, an analysis of available immunogenicity and safety results will be conducted. Analysis results with the safety data cutoff at 1 month after vaccination will be reviewed by the E-DMC. Additionally, the IRC will review safety data summaries prior to the enrollment of the expanded cohort at the same dose level as well as the initiation of each dose escalation as planned. Data may also be summarized at other time points for regulatory purposes. No multiplicity adjustments will be applied for these assessments.

After the completion of the 6-month follow-up visit, a clinical study report (CSR) including all safety and immunogenicity data gathered from before to within the 6 months following investigational product will be issued.

#### **9.5. Data Monitoring Committee**

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

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### **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 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 subject chart. In these cases, data collected on the CRFs must match the data in 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, and 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.

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), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

### **12.3. Subject Information and Consent**

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. 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 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 is fully informed about the nature and objectives of the study and possible risks associated with participation.

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 document.

#### **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) in a timely manner. 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](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or [www.pfizer.com](http://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](http://www.clinicaltrials.gov)

Pfizer posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://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](http://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](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to [www.clinicaltrials.gov](http://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

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

Abbreviation	Term
ABCs	Active Bacterial Core surveillance
ACIP	Advisory Committee on Immunization Practices (United States)
AE	adverse event
AlPO4	aluminum phosphate
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CK	creatinine kinase
CPS	capsular polysaccharide
CRF	case report form
CCI	
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
EC	ethics committee
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EOD	early-onset disease
EU	European Union
FDA	Food and Drug Administration (United States)
FIH	first-in-human
FSH	follicle-stimulating hormone
GBS	group B streptococcus
GBS6	group B streptococcus 6-valent CCI vaccine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
CCI	
HBV	hepatitis B virus
HIV	human immunodeficiency virus
IAP	intrapartum antibiotic therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation

<b>Abbreviation</b>	<b>Term</b>
ID	identification
IgG	immunoglobulin G
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
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
CCI	
PCD	primary completion date
PDA	personal digital assistant
PI	principal investigator
PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
CCI	
SRSD	single reference safety document
Tbili	total bilirubin
Tdap	tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine
ULN	upper limit of normal
UK	United Kingdom
US	United States



## Document Approval Record

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A PHASE 1/2, RANDOMIZED, PLACEBO-CONTROLLED, OBSERVE R-BLINDED TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MULTIVALENT GROUP B STREPTOCOCCUS VACCINE IN HEALTHY ADULTS 18 TO 49 YEARS OF AGE

**Signed By:**

**Date(GMT)**

**Signing Capacity**

PPD

08-Sep-2017 18:47:40

Final Approval

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