A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE GIVEN AS A SERIES OF 2 INFANT DOSES AND 1 TODDLER DOSE IN HEALTHY INFANTS

Investigational Product Number:	PF-06482077
Investigational Product Name:	20-valent Pneumococcal Conjugate Vaccine (20vPnC)
United States (US) Investigational New Drug (IND) Number:	CCI
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Protocol Number:	B7471012
Phase:	3

Short Title: 20-valent Pneumococcal Conjugate Vaccine Safety and Immunogenicity Study of a 3-Dose Series in Healthy Infants

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Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 2	18 June 2021	- Clarified the timing of collection of SAEs and NDCMCs in the safety estimands.
		- Added the noninferiority of IgG GMCs and the percentage of participants with predefined thresholds after 2 infant doses as primary immunogenicity objectives, and moved the objective for IgG percentage of participants with predefined thresholds after the toddler dose to the secondary objective, based on Scientific Advice from the CHMP. The statistical sections for these objectives were updated accordingly.
		- Removed "serotype-specific" from several immunogenicity estimands and endpoints.
		- Deleted 2 secondary pneumococcal immunogenicity objectives as they were moved up to the primary immunogenicity objectives, and revised the estimands for the remaining objective.
		- Removed a secondary objective to describe OPA GMTs before Dose 3, as it was part of the objective for OPA GMFR from before Dose 3 to 1 month after Dose 3.
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		- Clarified wording regarding the use of antipyretic/pain medication.
		- Updated safety language to match the current protocol template.
		- Added a WHO reference to the reference list to support the table on the Russian NIP.

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		- Sections 4.1 and 8: Added text regarding alternate options for visits due to the pandemic.
		- Section 6.5.3: Added clarification that a birth dose of hepatitis B vaccine is permitted.
		- Sections 8.3.6 and 8.3.6.1: Added sections to match the current protocol template.
		- Section 9: Made various revisions to the analyses of the data and the definitions of the study populations.
		- Section 9.1.2.1.3: Added text to describe hypothesis testing for IgGs 1 month after Dose 3.
		Section 9.1.3: Clarified that this section relates specifically to the primary immunogenicity evaluations.
		- Section 10.9: Added a country-specific appendix for Italy to clarify exclusion criterion 1 and the route of administration of concomitant study vaccines.
		- Section 10.10: Added a country-specific appendix for a Russian cohort to add approximately 60 participants, and address comments from a national agency on the schedule, concomitant vaccines, and other study aspects, including management of Russian cohort data. - Made updates throughout the protocol on managing the Russian cohort.
Amendment 1	13 April 2020	- Added the pneumococcal immunogenicity objectives comparing serotype-specific IgG concentrations 1 month after Dose 3 from the 20vPnC group to the 13vPnC group based on regulatory agency feedback. The statistical hypotheses, sample size determination, and statistical analyses for these objectives were updated accordingly.
		- Modified the concomitant administration of MMR and varicella vaccines (given at

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		Visit 4) to allow greater flexibility with accepted local practice.
		- Method of body temperature measurement at the investigator site has been made more flexible (standard method beyond axillary measurement is also allowed).
		- Name of the "Clinical Trial (CT) SAE Report Form was updated to "Vaccine SAE Reporting Form."
		- Section 1.1 Objectives, Estimands, and Endpoints, and Section 3: Editorial updates made to be consistent with other Phase 3 studies of 20vPnC.
		- Section 4.1: Minor update on wording of appearance of 20vPnC and 13vPnC was made for consistency with Section 6.1.
		- Section 6.5.1: Clarification to indicate that a fourth dose of Infanrix hexa is not permitted in the study.
		- Section 6.5.2: Clarified that rotavirus vaccine, if given, is to be administered according to local or national recommendations.
		- Section 8.1.1: CCI • Added a general description of the serum subsets for the concomitant vaccines including MMR and varicella.
		- Section 8.3.7 and Section 10.8: Mandatory protocol template text updates.
		- Section 8.10: Added "The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of ongoing safety review" to each vaccination visit as a reminder.

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		- Section 9.3: Updated the safety population definitions to be consistent with other Phase 3 studies of 20vPnC.
Original protocol	11 February 2020	Not applicable (N/A)

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

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Pfizer is developing a new 20-valent pneumococcal conjugate vaccine (20vPnC) candidate to expand protection against pneumococcal disease beyond that covered by current pneumococcal vaccines in children. 20vPnC has the same composition as 13-valent pneumococcal conjugate vaccine (13vPnC; Prevnar 13®/Prevenar 13®), but contains an additional 7 polysaccharide conjugates targeting serotypes responsible for a substantial burden of remaining pneumococcal disease. 20vPnC uses the same platform and contains the same excipients as 13vPnC. Phase 2 safety and immunogenicity data in infants support further development of 20vPnC in the pediatric population.

This Phase 3, multicenter, randomized, double-blind study will be conducted at investigator sites in the EU and Australia. Additional sites in Russia are also being sought. CCI CCI CCI The purpose of the study is to generate data on the safety and immunogenicity of 20vPnC in infants when administered in a series of 2 infant doses and 1 toddler dose. Data will also be generated on key routine pediatric vaccines given concomitantly with 20vPnC or 13vPnC. The primary study population will consist of approximately 1200 infants at >36 weeks of gestation and ≥42 to ≤112 days of age at the time of consent by a parent(s)/legal guardian(s). Participants will be randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) at 2, 4, and 11 to 12 months of age (Doses 1 [Visit 1], 2 [Visit 2], and 3 [Visit 4], respectively). Participants will receive the same vaccine (either 20vPnC or 13vPnC) for all 3 doses. CCI CCI

In order to expand the study to describe the safety and immunogenicity of 20vPnC in infants from Russia, approximately 60 Russian infants will be enrolled in the study, and referred to as the Russian cohort. The Russian cohort will not be included in the primary study population. This is a result of enrollment and subsequent visits in the primary study population anticipated to be complete several months before those in the Russian cohort, and based on some differences in concomitant vaccine schedule and visit windows in the Russian participants, reflecting the Russian NIP, described in Section 10.10 of this protocol. The safety and immunogenicity results in the Russian cohort will be summarized in a supplemental CSR.

The specific vaccine containing diphtheria, tetanus, acellular pertussis, hepatitis B, poliovirus, and *Haemophilus influenzae* type b (hereafter referred to as DTaP, HBV, IPV, and Hib or Infanrix hexa) antigens will be administered concomitantly with all doses of 20vPnC or 13vPnC (at Visits 1, 2, and 4) into a limb other than the site of 20vPnC or 13vPnC injection.

The specific vaccine containing measles, mumps, and rubella (MMR) antigens and the specific vaccine containing varicella antigen are also to be administered concomitantly with

Dose 3 (Visit 4) into a limb other than the site of 20vPnC or 13vPnC injection. These vaccines are intended to be given to all participants. However, in case of circumstances due to local practice/recommendations, some sites may not administer them to their participants at Dose 3, in which case MMR and varicella vaccines will be considered nonstudy vaccines.

Local reactions (including redness, swelling, and pain at the injection site), systemic events (including fever, drowsiness/increased sleep, decreased appetite, and irritability), and use of pain/fever medication will be prompted for and collected by the participant's parent(s)/legal guardian(s) daily for 7 days after each study vaccination (where Day 1 is the day of vaccination) in an electronic diary (e-diary).

Adverse events (AEs) will be recorded and reported from the signing of the informed consent document (ICD) through approximately 1 month after Dose 2 (Visit 3) and from Dose 3 (Visit 4) through approximately 1 month after Dose 3 (Visit 5).

Serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) will be collected from the signing of the ICD through 1 month after Dose 3 (Visit 5).

Blood will be drawn from all participants for immunogenicity assessments 1 month after Dose 2 (5 months of age, Visit 3), prior to receipt of Dose 3 (11-12 months of age, Visit 4), and 1 month after Dose 3 (13 months of age, Visit 5). A subset of participants (participants at certain investigator sites) will also have blood drawn for immunogenicity assessments prior to Dose 1 and prior to Dose 2.

Objectives, Estimands, and Endpoints

Primary Safety Objective	Estimands	Primary Safety Endpoints
To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination in each vaccine group: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination • The percentage of participants reporting prompted systemic events within 7 days after each vaccination • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3 • The percentage of participants reporting SAEs through 1 month after Dose 3	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs

	• The percentage of participants reporting NDCMCs through 1 month after Dose 3	
Primary Pneumococcal Immunogenicity Objectives	**Estimands**	**Primary Pneumococcal Immunogenicity Endpoints**
To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for the 13 serotypes in the 20vPnC group are noninferior to those of the corresponding serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest among the 13 serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the lowest percentage of participants with predefined IgG concentrations among the 13 serotypes from the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to those for the corresponding serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 13 matched serotypes: GMR of IgG concentrations from the 20vPnC group to the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest among the 13 serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 7 additional serotypes in 20vPnC: GMR of IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to those for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of IgG concentrations from the 20vPnC group to the 13vPnC group	• Pneumococcal IgG concentrations

To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest among the 13 serotypes in the 13vPnC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: GMR of IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal IgG concentrations
Primary Concomitant Immunogenicity Objective	**Estimands**	**Primary Concomitant Immunogenicity Endpoints**
To demonstrate that the immune responses induced by concomitant vaccine antigens given with 20vPnC are noninferior to immune responses induced by concomitant vaccine antigens given with 13vPnC at 1 month after Dose 3	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib 1 month after Dose 3 between the 20vPnC and the 13vPnC groups • GMRs of antibody levels to measles, mumps, rubella, and varicella antigens from the 20vPnC group to the 13vPnC group 1 month after Dose 3	• Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) • Antibody levels to HBsAg • Antibody levels to poliovirus strains (types 1, 2, and 3) • Antibody levels to Hib • Antibody levels to measles, mumps, rubella, and varicella virus
Secondary Pneumococcal Immunogenicity Objective	**Estimands**	**Secondary Pneumococcal Immunogenicity Endpoints**
To further describe the immune responses induced by 20vPnC	In evaluable participants: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the 13vPnC group at 1 month after Dose 3 • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the lowest percentage of participants with predefined IgG concentrations among the 13 serotypes from the 13vPnC group at 1 month after Dose 3 • For each of the 20 serotypes in 20vPnC: OPA GMTs 1 month after	• Pneumococcal IgG concentrations • Pneumococcal OPA titers

	Dose 2 and 1 month after Dose 3 in each vaccine group • For each of the 20 serotypes in 20vPnC: GMFRs in IgG concentrations from before Dose 3 to 1 month after Dose 3 in each vaccine group	
Secondary Concomitant Immunogenicity Objective	**Estimand**	**Secondary Concomitant Immunogenicity Endpoints**
To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC	In evaluable participants who receive appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), poliovirus strains, and Hib 1 month after Dose 2 between the 20vPnC and the 13vPnC groups	• Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) • Antibody levels to poliovirus strains (types 1, 2, and 3) • Antibody levels to Hib

In addition to these objectives, estimands, and endpoints, the safety and immunogenicity of the pneumococcal immune responses are described for the Russian cohort (Section 10.10.3).

Number of Participants

Approximately 1200 participants will be enrolled in the primary study population.

An additional approximately 60 participants will be enrolled in the Russian cohort.

Approximate Duration of Participation for Each Participant

Each participant in the primary study population will participate in the study for approximately 11 months.

Participants in the Russian cohort will participate in the study for approximately 11 to 14 months (see Section 10.10 for details).

Statistical Methods

Safety Objective

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs, including SAEs and NDCMCs, for each vaccine group. A 3-tier approach will be used to summarize AEs for the primary study population.

Pneumococcal Immunogenicity Objectives

The primary pneumococcal immunogenicity objectives for the primary study population will be evaluated by formal hypothesis tests for noninferiority (NI) of 20vPnC to 13vPnC based on serotype-specific IgG results.

The NI for a serotype based on percentages of participants with predefined serotype-specific IgG concentrations at 1 month after Dose 2 will be declared if the lower bound of the 2-sided 95% confidence interval (CI) for the between-group difference in percentage (20vPnC – 13vPnC) is greater than –10% (10% NI margin) for that serotype. The NI for a serotype based on serotype-specific IgG GMCs at 1 month after Dose 2 will be declared if the lower bound of the 2-sided 95% CI for the IgG GMR of the 20vPnC group relative to the 13vPnC group is greater than 0.5 (2-fold NI margin) for that serotype. The NI of the IgG GMCs at 1 month after Dose 3 will be assessed in a similar way.

Additionally, pneumococcal immunogenicity will be further characterized. CCI

Concomitant Immunogenicity Objectives

The primary concomitant immunogenicity objective for the primary study population will be evaluated by formal hypothesis tests for NI of the 20vPnC group to the 13vPnC group. At 1 month after Dose 3, for each antigen of diphtheria toxoid, tetanus toxoid, pertussis (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib, NI will be declared if the lower bound of the 2-sided 95% CI for the difference in percentage (20vPnC – 13vPnC) of participants with prespecified antibody levels is greater than –10% (10% NI margin). At 1 month after Dose 3, NI for each of the antigens of measles, mumps, rubella, and varicella will be declared if the lower bound of the 2-sided 95% CI for the GMR of the 20vPnC group relative to the 13vPnC group is greater than 0.5 (2-fold NI criterion).

Concomitant immunogenicity for the primary study population will be further described using summary statistics for the percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), poliovirus strains, and Hib 1 month after Dose 2.

The Russian cohort data will be summarized descriptively and separately from the primary study population data (see Section 10.10.3).

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the Study Assessments and Procedures section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Please see Section 10.10.2 for the SoA for the Russian cohort.

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

Visit Number	**1**	**2**	**3**	**4**	**5**
Visit Description	**Dose 1 Visit**	**Dose 2 Visit**	**Dose 2 Follow-up Visit**	**Dose 3 Visit**	**Dose 3 Follow-up Visit**
Visit Window (Days)	**≥42 to ≤112 Days After Birth**	**42 to 63 Days After Visit 1**	**28 to 42 Days After Visit 2**	**335 to 386 Days of Age**	**28 to 42 Days After Visit 4**
Obtain informed consent	X				
Assign participant number via the IRT	X				
Review inclusion and exclusion criteria	X				
Record demography	X				
Perform clinical assessment, including medical history	X				
Record vaccine history	X				
Provide parent(s)/legal guardian(s) with a contact card	X				
Obtain prevaccination temperature (measured as appropriate for age)	X	X		X	
Record nonstudy vaccinations and concomitant medications[a]	X	X	X	X	X

Visit Number	1	2	3	4	5
Visit Description	**Dose 1 Visit**	**Dose 2 Visit**	**Dose 2 Follow-up Visit**	**Dose 3 Visit**	**Dose 3 Follow-up Visit**
Visit Window (Days)	**≥42 to ≤112 Days After Birth**	**42 to 63 Days After Visit 1**	**28 to 42 Days After Visit 2**	**335 to 386 Days of Age**	**28 to 42 Days After Visit 4**
Record vaccines administered during pregnancy and intrapartum antibiotic use (yes/no) (if available)	X[b]				
Review temporary delay criteria	X	X	X	X	X
Review continued eligibility		X	X	X	X
Assign randomization number	X				
Obtain ~5-mL blood sample	CCI	CCI	X	X[c]	X
Administer investigational product in the left thigh[e]	X	X		X	
Administer specific concomitant vaccines as applicable for visit	X[f]	X[f]		X[f,g]	
Observe and record any reactions for 30 minutes after investigational vaccine administration	X	X		X	
Provide parent(s)/legal guardian(s) with an e-diary (device or application, as appropriate), digital thermometer, and measuring device and instruct to collect prompted local reactions and systemic events 7 days after vaccination[h]	X	X		X	
Review e-diary[i]		X	X		X
Collect e-diary (if applicable)			X		X

Visit Number	1	2	3	4	5
Visit Description	**Dose 1 Visit**	**Dose 2 Visit**	**Dose 2 Follow-up Visit**	**Dose 3 Visit**	**Dose 3 Follow-up Visit**
Visit Window (Days)	**≥42 to ≤112 Days After Birth**	**42 to 63 Days After Visit 1**	**28 to 42 Days After Visit 2**	**335 to 386 Days of Age**	**28 to 42 Days After Visit 4**
Record and report AEs[j]	X----------X			X ----------X	
Record and report SAEs and NDCMCs[j,k]	X----------X				

Abbreviations: DTaP = diphtheria, tetanus, and acellular pertussis vaccine; e-diary = electronic diary; HBV = hepatitis B virus; Hib = *Haemophilus influenzae* type b; IPV = inactivated poliovirus vaccine; IRT = interactive response technology; NDCMC = newly diagnosed chronic medical condition.

a. Record concomitant medications used to treat SAEs and NDCMCs from the signing of the ICD to the final visit (Visit 5) .
b. Vaccines administered during pregnancy and intrapartum antibiotic use (yes or no) will be collected at Visit 1 only (if available).
c. Blood sample will be collected prior to vaccination.

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e. Remind the participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.
f. The participant will receive a specific vaccine containing DTaP, HBV, IPV, and Hib antigens at approximately 2, 4, and 11 to 12 months of age (Visit 1, Visit 2, and Visit 4, respectively). This vaccine(s) will be given in a limb other than the site of administration of 20vPnC or 13vPnC.
g. Specific concomitant vaccines containing measles, mumps, rubella (MMR) and varicella antigens are also to be administered at approximately 11 to 12 months of age with Dose 3 (Visit 4). These vaccines will be administered in a limb other than the site of administration of 20vPnC or 13vPnC and are intended to be given to all participants. However, in case of circumstances due to local practice/recommendations, some sites may not administer them to their participants with Dose 3, in which case MMR and varicella vaccines will be considered nonstudy vaccines.
h. The participant's parent(s)/legal guardian(s) will record prompted local reactions and systemic events in an e-diary for the 7 days following each dose of 20vPnC or 13vPnC. Use of antipyretic/pain medications will also be prompted for and collected daily in the e-diary for 7 days after vaccination. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling >14 caliper units, severe pain at the 20vPnC or 13vPnC injection site, a fever >40.0°C (>104.0°F), an emergency room visit, or hospitalization.
i. Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 7 days following each dose of 20vPnC or 13vPnC to evaluate participant compliance and reported events as part of the ongoing safety review.
j. If the parent(s)/legal guardian(s) consents, participants withdrawn from the study will have any new AEs, SAEs, and NDCMCs collected for 1 month after their last study vaccination.
k. An NDCMC is a significant disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects.

2. INTRODUCTION

Pneumococcal Disease

Streptococcus pneumoniae are gram-positive encapsulated cocci that are a leading cause of bacteremia, bacterial meningitis, pneumonia, and acute otitis media (AOM) and continue to be a major global public health concern.[1,2,3] Serious pneumococcal disease may occur at any age; however, children <5 years and adults ≥65 years of age are at particularly increased risk.[4] Individuals with certain comorbidities and immunocompromising conditions are also at risk, especially persons with chronic heart, lung, liver, and renal disease, as well as those who are functionally asplenic. The global burden of pneumococcal disease has been substantially impacted by pneumococcal conjugate vaccines. *S pneumoniae* caused an estimated 14.5 million cases of serious disease and 826,000 deaths annually in children <5 years of age prior to introduction of pneumococcal conjugate vaccines.[2] It has been estimated that in 2015, several years following introduction of pneumococcal conjugate vaccines into the national infant immunization programs of more than 100 countries, the global disease burden had declined, but *S pneumoniae* still accounted for 2.6 million cases of severe pneumococcal disease, 332,000 deaths in children <5 years of age, and 11% of deaths in children between the ages of 1 and 5 years.[5]

The overall invasive pneumococcal disease (IPD) burden was estimated in 2013 to have decreased approximately 90% in the population <5 years of age in the United States since the introduction of pneumococcal conjugate vaccines; however, there was a slight increase in the proportions of IPD cases associated with hospitalization (63% to 71%), and the IPD case fatality rate was also slightly but statistically significantly increased (2% to 3%) in that age group.[6] This is due to the decrease in disease due to the serotypes in 7-valent pneumococcal conjugate vaccine (7vPnC; Prevnar®/Prevenar®) and 13vPnC. However, disease due to serotypes not covered by those vaccines remains and causes significant morbidity and mortality.

National IPD surveillance data in England and Wales for the epidemiological year 2016-2017, approximately 10 years after the introduction of 7vPnC in the national infant immunization program and 6 years after the introduction of 13vPnC, the overall incidence of IPD was 9.87 per 100,000 population, with an incidence of 13.90 per 100,000 population <2 years of age.[7] The data for England and Wales are consistent with the patterns observed in data from the European Union (EU) for 2017, which showed an overall IPD incidence of 6.2 cases per 100,000 population, with an incidence of 14.5 per 100,000 infants under 1 year of age.[8] Pediatric surveillance studies conducted between 2007 and 2013 in 8 US children's hospitals, and between 1997 and 2010 in a referral center in Utah, found case fatality rates of 10% and 13% with pneumococcal meningitis, respectively. These studies also found that between 52% and 63% of children surviving pneumococcal meningitis experience neurologic sequelae.[9,10] More recent pediatric surveillance conducted between 2014 and 2017 in 8 US children's hospitals following 13vPnC introduction in 2010 showed that 76.1% of residual IPD was caused by non-13vPnC serotype isolates. Serotypes 10A, 12F, 15B/15C, 22F, and 33F accounted for 36% of isolates causing IPD.

The most common clinical presentations of IPD due to non-13vPnC serotypes included bacteremia (49.6%), meningitis (19.1%), and pneumonia (18.8%).[11] These data demonstrate the continued need for expanded serotype coverage.

Surveillance studies conducted in 2010-2012 by the Centers for Disease Control and Prevention (CDC) found that *S pneumoniae* remains among the most common pathogens identified in community-acquired pneumonia (CAP) requiring hospitalization in the United States in both children and adults.[12,13] It was the most common bacterial cause in children <2 years of age, even in the setting of a 43% reduction in CAP hospitalizations over the previous decade between 1997-1999 and 2007-2009, due to the introduction to 7vPnC.[12,14]

Surveillance reported in 2017 by the European Centre for Disease Prevention and Control (ECDC) showed that among cases of IPD for which the clinical presentation was known across all age groups, septicemia was reported in 35%, bacteremic pneumonia in 42%, meningitis in 19%, meningitis and septicemia in 1%, and other clinical syndromes in 3% of cases. The most common clinical presentations in children <5 years of age were septicemia and bacteremic pneumonia equally (1-4 year olds), and meningitis (<1 year olds).[8] Data from nationwide surveillance networks in France for the year 2012 showed the rate of IPD among children <2 years of age to be 17.2 per 100,000 population, with the incidence of pneumococcal meningitis among children <2 years of age to be 4.5 per 100,000 population. Of note, meningitis comprised 26.4%, 7.8%, and 19.6% of all cases of IPD in children <2 years of age, 2 through 4 years of age, and 5 through 15 years of age, respectively.[15] The relatively high rates of meningitis among these pediatric populations are of particular concern not only because of the severity of the acute disease, but also because of the neurological sequelae that are frequently associated with meningitis. These data suggest that *S pneumoniae* remains an important cause of serious disease in the United States and worldwide.

AOM is a common childhood illness, with 2011 visit rates of 0.82 and 0.81 visits for AOM/child-year in children <2 years of age and 2 to 6 years of age, respectively, and represents a significant medical burden.[16] *S pneumoniae* is one of the common bacterial causes of AOM, and accounted for an estimated 850,000 outpatient and 125,000 emergency room visits in the United States in 2004 in children <5 years of age, representing a significant burden on the healthcare system.[3] While AOM is generally not considered a serious disease, it does carry the risk of more serious complications. These complications can range from the development of chronic or recurrent otitis media necessitating surgical intervention (tympanostomy tube placement), and accompanied by hearing losses with potential developmental and language delays, to invasive extension leading to mastoiditis and meningitis.

Although the introduction of pneumococcal conjugate vaccines into the United States and other national infant immunization programs has brought about substantial reductions in the various manifestations of pneumococcal disease in pediatric (infants and children) populations, a substantial burden of pneumococcal disease remains. Serotypes not included in existing vaccines continue to contribute significantly to morbidity and mortality.

Vaccines to Prevent Pneumococcal Disease

Pneumococcal Polysaccharide Vaccines

The polysaccharide capsule has been identified as an important virulence factor for this pathogen. While more than 95 pneumococcal serotypes, differentiated by their capsular polysaccharide composition, have been identified, serious disease is generally caused by a smaller subset of serotypes.[17,18] Anticapsular antibodies directed against the specific serotype bind to the capsule and promote complement-mediated opsonophagocytic killing and clearance of the organism.[19] Pneumococcal disease can be prevented with polysaccharide-based vaccines that induce antibody responses with functional (opsonophagocytic) activity and target the capsular serotypes responsible for disease.[20]

Vaccines containing free polysaccharides have been licensed since the 1970s. One such vaccine, the 23-valent pneumococcal polysaccharide vaccine (PPSV23), has been licensed in the United States since 1983.[21,22] PPSV23 contains capsular polysaccharides for 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). Pneumococcal vaccines containing free polysaccharides such as PPSV23 elicit a T-cell–independent immune response. Unconjugated polysaccharide vaccines do not induce robust responses in certain populations (eg, immunocompromised persons, and children <2 years of age), nor do they generate immunologic memory, so that their protective effect wanes over 2 to 5 years.[4,22,23,24] Moreover, their ability to prevent nonbacteremic pneumonia, CAP, and AOM is limited or lacking.[20,24,25,26,27] In addition, polysaccharide vaccines do not reduce vaccine-type (VT) nasopharyngeal carriage, which is important for herd immunity.[27] PPSV23 is not recommended for children <2 years of age and only recommended in children >2 years of age who are at high risk for IPD to provide some degree of protection from disease caused by serotypes not covered by existing pneumococcal conjugate vaccines.[20]

Pneumococcal Polysaccharide Conjugate Vaccines

Pneumococcal conjugate vaccines contain polysaccharides that are covalently linked (conjugated) to an immunogenic protein. This modification results in T-cell–dependent immune responses, which have been shown to be protective in young children, older adults, and populations with high-risk conditions.[23,28] 7vPnC was the first pneumococcal conjugate vaccine to be licensed (2000) and was indicated for prevention of pneumococcal disease in infants and young children on the basis of efficacy studies. 7vPnC contained capsular polysaccharide conjugates for 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), each covalently linked to cross-reactive material 197 (CRM_{197}), a nontoxic variant of diphtheria toxin. These 7 serotypes were responsible for approximately 80% to 90% of IPD in children <5 years of age in the United States and approximately 60% to 80% of IPD in the same age group in Europe at that time (1998-2000).[29,30,31,32,33] These serotypes also accounted for a high proportion of antibiotic-resistant strains.[34] 7vPnC demonstrated efficacy against VT IPD, pneumonia, and AOM in large randomized, controlled efficacy studies in infants.[35,36]

The 7vPnC components contained in a related pneumococcal conjugate vaccine also were demonstrated to be efficacious against clinically/radiographically defined pneumonia.[37,38,39,40] Following introduction of 7vPnC, reduction of nasopharyngeal carriage and transmission has resulted in indirect herd effects, with a 92% reduction of 7vPnC VT IPD in older adults ≥65 years of age.[41]

13vPnC was developed to expand serotype coverage and was licensed in the United States in 2010. In the EU, 13vPnC was initially indicated for use in infants from 6 weeks to 5 years of age, but the indication was later expanded to include children and adolescents up to 17 years of age. 13vPnC includes the same *S pneumoniae* serotypes as 7vPnC and an additional 6 polysaccharide conjugates for serotypes 1, 3, 5, 6A, 7F, and 19A.[28,32,42] The vaccine was licensed for use in infants and young children based on comparisons of serotype-specific serum IgG antibody concentrations to 7vPnC, with supportive data to demonstrate the functional activity of the immune responses. 13vPnC was later licensed in adults based on demonstration of efficacy against CAP due to serotypes contained in 13vPnC in adults 65 years of age and older.[43] 13vPnC has replaced 7vPnC and is licensed in the United States and many other countries, with national recommendations for use in children and older adults.[44,45,46,47] It has also been prequalified by the World Health Organization (WHO) for use in national infant immunization programs in lower- and middle-income countries.[48,49] Surveillance data from several countries following introduction of 13vPnC into the routine infant immunization program have demonstrated vaccine effectiveness against 13vPnC VT IPD in the vaccinated population.[50,51,52]

Development of 20vPnC

The 20vPnC candidate is modeled after 7vPnC and 13vPnC, and contains polysaccharides of capsular serotypes of *S pneumoniae*, each covalently linked to CRM_{197}. The amount of polysaccharide (2.2 µg/dose) selected for each new serotype (8, 10A, 11A, 12F, 15B, 22F, and 33F) contained in the 20vPnC candidate mirrors the approach taken for the addition of the 6 new serotypes when developing 13vPnC. The 20vPnC candidate contains the same components as 13vPnC, including the 13 polysaccharide conjugates, excipients (polysorbate 80, succinate buffer, sodium chloride), and aluminum phosphate, in addition to the 7 new polysaccharide conjugates. Additional epidemiology data of the 7 serotypes and the preclinical program are described in the 20vPnC investigator's brochure (IB). The vaccine is being developed for use in pediatric and adult populations.

2.1. Study Rationale

CCI [redacted] CCI The targeted age of the population for this study, infants born at >36 weeks of gestation and ≥42 to ≤112 days of age, has been selected as the routinely recommended vaccination schedule for pneumococcal conjugate vaccines and other vaccines in infants, starting at approximately 2 months of age.

The participants will be administered either 20vPnC or 13vPnC in a series of 2 infant doses and 1 toddler dose (at 2, 4, and 11-12 months of age). Data will also be generated on key routine pediatric vaccines given concomitantly with 20vPnC or 13vPnC.

2.2. Background

20vPnC is being developed to further expand protection against the global burden of vaccine-preventable pneumococcal disease in children and adults over that of 13vPnC. 20vPnC contains the serotypes present in 13vPnC, and 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) individually conjugated to CRM_{197}. As noted above, 20vPnC uses the same platform and contains the same excipients as 7vPnC and 13vPnC. These 7 additional serotypes were selected based on their relative prevalence as a cause of IPD, their generalized geographic distribution, and other factors that would support inclusion, such as the presence of antibiotic resistance (11A, 15B), association with outbreaks (8, 12F), and greater disease severity (eg, meningitis, mortality) (10A, 11A, 22F).[53,54,55,56,57,58,59,60,61,62,63,64] These 7 serotypes have a long-standing association with serious pneumococcal disease and are responsible for a substantial burden of remaining pneumococcal disease.

The incidence of IPD due to these 7 serotypes in children <5 years of age has remained relatively stable or slightly increased over the past several years, and these serotypes cause a significant amount of IPD in children.[65,66,67,68,69,70,71] These 7 serotypes contribute to the burden of IPD in the United States and elsewhere. It is estimated that between 2015 and 2016, these 7 serotypes accounted for 34% to 39% of IPD in children in the United States.[72] In the EU, according to the ECDC annual IPD epidemiological report, in 2017, approximately 75% of cases in children <5 years of age were caused by a serotype not in 13vPnC, increased from 63% in 2013. Five of the 10 most common serotypes included serotypes 8, 10A, 11A, 12F, and 22F, with serotypes 8, 10A, 12F, and 24F being among the most common in children in this age group.[8]

A meta-analysis of serotypes causing IPD in children <5 years of age in regions of the world that have introduced higher-valent pneumococcal conjugate vaccines (such as 13vPnC) showed that, overall, these 7 serotypes accounted for approximately 70% of disease not due to the 13vPnC vaccine types.[67]

2.2.1. Clinical Overview

Safety and immunogenicity data from a 20vPnC Phase 1 study (B7471001) conducted in healthy adults 18 to 49 years of age demonstrated that the vaccine induces immune responses to the 20 vaccine serotypes and has a safety profile consistent with other pneumococcal conjugate vaccines. These data supported clinical development in other populations, including pediatrics.

A Phase 2 study (B7471003) of 20vPnC in healthy infants was started in April 2018. In the study, 460 US participants ≥42 to ≤98 days of age were randomized to receive either blinded 20vPnC or 13vPnC. The study is currently ongoing, but safety and immunogenicity data are available from the study.

20vPnC was well tolerated in the infants and the safety profile was similar to that of the 13vPnC group in the study and consistent with other pneumococcal conjugate vaccines. Immune responses (either IgG GMCs or percentages of participants meeting a predefined IgG concentration) after 3 doses of 20vPnC were similar to those in the 13vPnC group. These data support continued development of 20vPnC in the pediatric population.

2.3. Benefit/Risk Assessment

13vPnC is a licensed vaccine and the most common AEs noted in children <5 years of age after vaccination are primarily related to local reactions (injection site pain or tenderness, redness, and swelling) and systemic events (fever, irritability, decreased appetite, and increased sleep).

The 20vPnC investigational product contains the same components and excipients as 13vPnC, along with the polysaccharide conjugates for the 7 additional pneumococcal serotypes. Thus, the AE profile of 20vPnC is expected to be similar to 13vPnC, but AEs may be different with the investigational 20vPnC.

In a randomized, active-controlled, double-blind study with a 2-arm parallel design (B7471003), 20vPnC was administered to 460 infants ≥42 to ≤98 days of age naïve to pneumococcal vaccine. The vaccine was well tolerated and the AE profile was consistent with events commonly seen in this age group. The most common AEs after 20vPnC administration were local reactions (pain, redness, and swelling at the injection site) and systemic events (irritability, drowsiness/increased sleep, and decreased appetite).

As with any vaccine, an allergic reaction can occur. The allergic reaction can vary from skin rash to swelling of the face or lips, wheezing, and/or shortness of breath. A severe allergic reaction (anaphylactic shock, collapse, or shock-like state [hypotonic-hyporesponsive episode]) may also occur. There may also be additional risks related to the vaccines administered in the study that are not known at this time.

The most common adverse reactions observed after administration of a specific vaccine containing DTaP, HBV, IPV, and Hib antigens were loss of appetite, abnormal crying, irritability, restlessness, fever, fatigue, and injection site reactions including swelling, pain, and redness.

The most common adverse reactions observed after administration of a specific MMR vaccine were fever, injection site reactions including pain, swelling, bruising, and redness, rash, and upper respiratory tract infection.

The most common adverse reactions observed after administration of a specific varicella vaccine were injection site pain, redness, and swelling, fever, rash, upper respiratory tract infection, and irritability.

Risks that may be associated with study procedures include risks from blood draws, including pain, swelling, bruising, and infection where blood is taken. Safety assessments described in the protocol and ongoing review of safety data by the investigator and sponsor study team will serve to monitor and mitigate these risks. CCI

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13vPnC is approved for the prevention of pneumococcal disease due to the serotypes in the vaccine, and may provide a clinical benefit to those receiving it.

In the B7471003 study, 20vPnC induced immune responses to the pneumococcal serotypes in the vaccine. This suggests that protection against pneumococcal disease will be similar to 13vPnC. If 20vPnC is successful in Phase 3 studies, and approved, it is anticipated to provide a public health benefit by reducing the burden of pneumococcal disease (invasive and noninvasive) due to vaccine serotypes.

Pfizer considers that the available information from Study B7471003 with 20vPnC, the available safety profile of similar pneumococcal conjugate vaccines (ie, 7vPnC and 13vPnC), and the limited risks from study procedures support a favorable benefit-risk profile for 20vPnC and this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of 20vPnC may be found in the IB, which is the single reference safety document (SRSD) for this study. The SRSD for the 13vPnC active comparator vaccine is the EU summary of product characteristics (SmPC). The SRSD for the vaccine containing DTaP, HBV, IPV, and Hib, the MMR vaccine, and the varicella vaccine is the EU SmPC.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Primary Safety Objective	Estimands	Primary Safety Endpoints
To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination in each vaccine group: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination • The percentage of participants reporting prompted systemic events within 7 days after each vaccination • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3 • The percentage of participants reporting SAEs through 1 month after Dose 3	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs

	• The percentage of participants reporting NDCMCs through 1 month after Dose 3	
Primary Pneumococcal Immunogenicity Objectives	**Estimands**	**Primary Pneumococcal Immunogenicity Endpoints**
To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for the 13 serotypes in the 20vPnC group are noninferior to those of the corresponding serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest among the 13 serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the lowest percentage of participants with predefined IgG concentrations among the 13 serotypes from the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to those for the corresponding serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 13 matched serotypes: GMR of IgG concentrations from the 20vPnC group to the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest among the 13 serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 7 additional serotypes in 20vPnC: GMR of IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of IgG concentrations from the 20vPnC group to the 13vPnC group	• Pneumococcal IgG concentrations

To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest among the 13 serotypes in the 13vPnC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: GMR of IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal IgG concentrations
Primary Concomitant Immunogenicity Objective	**Estimands**	**Primary Concomitant Immunogenicity Endpoints**
To demonstrate that the immune responses induced by concomitant vaccine antigens given with 20vPnC are noninferior to immune responses induced by concomitant vaccine antigens given with 13vPnC at 1 month after Dose 3	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib 1 month after Dose 3 between the 20vPnC and the 13vPnC groups • GMRs of antibody levels to measles, mumps, rubella, and varicella antigens from the 20vPnC group to the 13vPnC group 1 month after Dose 3	• Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) • Antibody levels to HBsAg • Antibody levels to poliovirus strains (types 1, 2, and 3) • Antibody levels to Hib • Antibody levels to measles, mumps, rubella, and varicella virus
Secondary Pneumococcal Immunogenicity Objective	**Estimands**	**Secondary Pneumococcal Immunogenicity Endpoints**
To further describe the immune responses induced by 20vPnC	In evaluable participants: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the 13vPnC group at 1 month after Dose 3 • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the lowest percentage of participants with predefined IgG concentrations among the 13 serotypes from the 13vPnC group at 1 month after Dose 3 • For each of the 20 serotypes in 20vPnC: serotype-specific OPA GMTs 1 month after Dose 2 and	• Pneumococcal IgG concentrations • Pneumococcal OPA titers

	1 month after Dose 3 in each vaccine group • For each of the 20 serotypes in 20vPnC: GMFRs in IgG concentrations from before Dose 3 to 1 month after Dose 3 in each vaccine group	
Secondary Concomitant Immunogenicity Objective	**Estimand**	**Secondary Concomitant Immunogenicity Endpoints**
To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC	In evaluable participants who receive appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), poliovirus strains, and Hib 1 month after Dose 2 between the 20vPnC and the 13vPnC groups	• Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) • Antibody levels to poliovirus strains (types 1, 2, and 3) • Antibody levels to Hib

[redacted]

(For Russian cohort–specific objectives, estimands, and endpoints, please see Section 10.10.3)

4. STUDY DESIGN

4.1. Overall Design

This Phase 3, multicenter, randomized, double-blind study will be conducted at investigator sites in the EU and Australia. Additional sites in Russia are also being sought to generate data in infants from that country. CCI CCI The purpose of the study is to generate data on the safety and immunogenicity of 20vPnC in infants when administered in a series of 2 infant doses and 1 toddler dose (at 2, 4, and 11-12 months of age). Data will also be generated on key routine pediatric vaccines given concomitantly with 20vPnC or 13vPnC. 13vPnC will serve as an active comparator.

Approximately 1200 infants >36 weeks of gestation and ≥42 to ≤112 days of age at the time of consent by a parent(s)/legal guardian(s) will be enrolled in the primary study population of the study. Participants will be randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) by site-based randomization. At 2, 4, and 11 to 12 months of age (Doses 1 [Visit 1], 2 [Visit 2], and 3 [Visit 4], respectively), participants will receive the

same vaccine (either 20vPnC or 13vPnC) for all 3 doses. Blood will be drawn from all participants for immunogenicity assessments 1 month after Dose 2 (5 months of age), prior to receipt of Dose 3 (11-12 months of age), and 1 month after Dose 3 (13 months of age). A subset of participants (participants at certain investigator sites) will also have blood drawn for immunogenicity assessments prior to Dose 1 and prior to Dose 2.

The Russian cohort will not be included in the primary study population, as the enrollment and subsequent visits in the primary study population are anticipated to be complete several months before the Russian cohort, and the concomitant vaccine schedule and visit windows are slightly different, reflecting the Russian NIP; these details are described in Section 10.10 of this protocol. The safety and immunogenicity results in the Russian cohort will be summarized in a supplemental CSR.

On Day 1 (Visit 1, Dose 1 vaccination) of the study, participants will be assessed for eligibility and information will be collected, including medical history and vaccine history. Vaccines administered during pregnancy and intrapartum antibiotic use (yes/no) will also be collected (if available). In a subset of participants (participants at selected investigator sites), blood will be drawn prior to Dose 1. All participants will receive Dose 1 of 20vPnC or 13vPnC. The 13vPnC and 20vPnC will be matched in appearance and will be prepared and administered by a site staff member or designee. Specific concomitant vaccination containing DTaP, HBV, IPV, and Hib antigens (Infanrix hexa) will also be administered at this visit. Participants will be observed for 30 minutes after vaccination, and any reactions occurring during that time will be recorded as AEs.

The participant's parent(s)/legal guardian(s) will be provided with an e-diary (or e-diary application), digital thermometer, and measuring device and instructed to collect prompted local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) occurring 7 days after each vaccination. Use of antipyretic/pain medications will also be prompted for and collected daily in the e-diary for 7 days after vaccination. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling >14 caliper units, severe pain at the 20vPnC or 13vPnC injection site, or fever >40.0°C (>104.0°F) in the 7 days after vaccination, or has an emergency room visit or hospitalization.

Participants will return for Visit 2 (42 to 63 days after Visit 1). Participants will be assessed for continued eligibility and information will be collected from the participant's parent(s)/legal guardian(s) on AEs, including nonserious AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs and NDCMCs will be recorded, as will information on nonstudy vaccinations given since the last visit. An NDCMC is defined as a significant disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects. A subset of participants will have blood drawn for immunogenicity assessment at this visit prior to Dose 2. Dose 2 of 20vPnC or 13vPnC will be administered. Specific concomitant vaccination containing DTaP, HBV, IPV, and Hib antigens will also be administered at this visit. Participants will be observed for 30 minutes after vaccination and any reactions

occurring during that time will be recorded as AEs. The participant's parent(s)/legal guardian(s) will be instructed to collect prompted local reactions and systemic events occurring 7 days after vaccination. Use of antipyretic/pain medications will also be prompted for and collected daily in the e-diary for 7 days after vaccination. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling >14 caliper units, severe pain at the 20vPnC or 13vPnC injection site, or fever >40.0°C (>104.0°F) in the 7 days after vaccination or has an emergency room visit or hospitalization.

Participants will return for Visit 3 (28 to 42 days after Visit 2). Participants will be assessed for continued eligibility and information will be collected from the participant's parent(s)/legal guardian(s) on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). The e-diary will be collected (if applicable). Concomitant medications used to treat SAEs and NDCMCs will be recorded, as will information on nonstudy vaccinations given since the last visit. Blood will be taken for immunogenicity assessment.

Participants will return for Visit 4 (335 to 386 days of age). Participants will be assessed for continued eligibility and information will be collected from the participant's parent(s)/legal guardian(s) on SAEs and NDCMCs. Concomitant medications used to treat SAEs and NDCMCs will be recorded, as will information on nonstudy vaccinations given since the last visit. Blood will be taken for immunogenicity assessment prior to vaccination. Dose 3 will be administered at this visit. Specific concomitant vaccine containing DTaP, HBV, IPV, and Hib antigens will also be administered.

Specific vaccines containing MMR and varicella antigens are also to be administered at this visit. The MMR and varicella vaccines are intended to be given to all participants. However, in case of circumstances due to local practice/recommendations, some sites may not administer them to their participants at Dose 3, in which case MMR and varicella vaccines will be considered nonstudy vaccines. Participants will be observed for 30 minutes after vaccination and any reactions occurring during that time will be recorded as AEs. The participant's parent(s)/legal guardian(s) will be reissued an e-diary (if applicable). The participant's parent(s)/legal guardian(s) will be instructed to collect prompted local reactions and systemic events occurring 7 days after vaccination. Use of antipyretic/pain medications will also be prompted for and collected daily in the e-diary for 7 days after vaccination. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling >14 caliper units, severe pain at the 20vPnC or 13vPnC injection site, or fever >40.0°C (>104.0°F) in the 7 days after vaccination, or has an emergency room visit or hospitalization.

All participants will return for Visit 5 (28 to 42 days after Visit 4). Information will be collected from the participant's parent(s)/legal guardian(s) on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs will be recorded, as will information on nonstudy vaccinations given since the last visit. Blood will be taken for immunogenicity assessment. Other licensed nonstudy vaccines may be administered after the blood draw at this visit.

In the case of extreme circumstances, such as natural disasters or a pandemic, visits for follow-up or procedures may need to be conducted through other means (eg, telephone calls).

(For Russian cohort–specific differences, please see Section 10.10.1.)

4.1.1. Approximate Duration of Participation for Each Participant

Each participant in the primary study population will participate in the study for approximately 11 months.

Participants in the Russian cohort will participate in the study for approximately 11 to 14 months (see Section 10.10).

4.1.2. Approximate Number of Participants

Approximately 1200 participants will be enrolled in the primary study population.

Approximately 60 additional participants will be enrolled in the Russian cohort.

4.2. Scientific Rationale for Study Design

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CCI Infants born at >36 weeks of gestation and ≥42 to ≤112 days of age will be eligible if they are naïve to pneumococcal vaccination. This study population has been selected as this is the historical population studied for licensure of 7vPnC and 13vPnC in infants. The participants will be administered either 20vPnC or 13vPnC at 2, 4, and 11 to 12 months of age. This is consistent with the current pneumococcal vaccine recommendations for infants in the EU.[32] 13vPnC will serve as the comparator to 20vPnC for assessment of safety and immunogenicity.

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In order to expand the study to describe the safety and immunogenicity of 20vPnC in infants from Russia, approximately 60 Russian infants will be enrolled in the study, and referred to as the Russian cohort. The Russian cohort will not be included in the primary study population. This is a result of enrollment and subsequent visits in the primary study population anticipated to be complete several months before those in the Russian cohort, and based on differences in concomitant vaccine schedule and visit windows in the Russian participants, reflecting the Russian NIP, described in Section 10.10 of this protocol. The safety and immunogenicity results in the Russian cohort will be summarized in a supplemental CSR.

4.3. Justification for Dose

The 20vPnC candidate is modeled after 7vPnC and 13vPnC, and contains capsular polysaccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM_{197}. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. In infants, administration of 2 doses of pneumococcal conjugate vaccine given in infancy at 2 and 4 months of age, and 1 dose given at 11 to 12 months of age, induces protective immune responses.

4.4. End of Study Definition

- Primary study population: The end of the study is defined as the date of the last visit of the last participant in the primary study population.

- Russian cohort: The end of the study is defined as the date of the last visit of the last participant in this cohort.

5. STUDY POPULATION

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

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female infants born at >36 weeks of gestation and 2 months of age (≥42 to ≤112 days) at the time of consent (the day of birth is considered day of life 1).

Type of Participant and Disease Characteristics:

2. Participants whose parent(s)/legal guardian(s) are willing and able to comply with all scheduled visits, treatment plan, and other study procedures.

3. Healthy infants determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study.

4. Expected to be available for the duration of the study and whose parents(s)/legal guardian can be contacted by telephone during study participation.

Informed Consent:

5. Participants whose parent(s)/legal guardian(s) is capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

   (See Section 10.10 for the Russian cohort enrollment age window.)

5.2. Exclusion Criteria

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

Medical Conditions:

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of investigational product or any diphtheria toxoid–containing vaccine.

2. Significant neurological disorder or history of seizure including febrile seizure or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Does not include resolving syndromes due to birth trauma, such as Erb's palsy and/or hypotonic-hyporesponsive episodes.

3. Major known congenital malformation or serious chronic disorder.

4. History of microbiologically proven invasive disease caused by *S pneumoniae*.

5. Known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, DiGeorge syndrome, generalized malignancy, human immunodeficiency virus (HIV) infection, leukemia, lymphoma, or organ or bone marrow transplant.

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

7. Congenital, functional, or surgical asplenia.

8. Other 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 participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

9. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.

10. Prior receipt of diphtheria, tetanus, pertussis, poliomyelitis, and/or Hib vaccine.

11. Currently receives treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

12. Receipt of blood/plasma products or immunoglobulins (including hepatitis B immunoglobulin) since birth or planned receipt through the last planned blood draw in the study (Visit 5, 1 month after Dose 3).

Prior/Concurrent Clinical Study Experience:

13. Participation in other studies involving investigational drug(s), investigational vaccines, or investigational devices within 28 days prior to study entry and/or during study participation or intrauterine exposure to investigational vaccines. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

14. Children or grandchildren who are direct descendants of investigator site staff members or Pfizer employees who are directly involved in the conduct of the study.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants whose parent(s)/legal guardian(s) have consented for them to participate in the clinical study but are not subsequently randomly assigned to investigational product/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs and SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

5.5. Temporary Delay Criteria

The following conditions are temporary or self-limiting and a participant may be vaccinated and/or have blood drawn in the study once the condition(s) has/have resolved and no other exclusion criteria are met.

The blood draws prior to vaccination should take place on the same day as the vaccination.

5.5.1. Criteria for Temporarily Delaying Vaccine Administration

- Current febrile illness (temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before investigational product administration.

- Receipt of any inactivated or otherwise nonlive vaccine within 14 days or any live vaccine within 28 days before investigational product administration (with the exception of licensed inactivated influenza vaccine, which may be given at any time during the study per national recommendations).

- Receipt of short-term (<14 days) systemic corticosteroids. Investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

5.5.2. Criteria for Temporarily Delaying Immunogenicity Blood Draw

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

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

For additional information for the Russian cohort, please see Section 10.10.4.

6.1. Study Intervention(s) Administered

20vPnC is a sterile liquid suspension formulation containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM_{197}. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contains 5 mM succinate buffer, 150 mM sodium chloride, 0.02% polysorbate 80, and 125 µg aluminum as aluminum phosphate, per 0.5-mL dose.

13vPnC is a sterile liquid suspension formulation containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to CRM_{197}. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contains 295 µg succinate buffer, 0.85% sodium chloride, 100 µg polysorbate 80, and 125 µg aluminum as aluminum phosphate, per 0.5-mL dose.

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20vPnC and 13vPnC, supplied as syringes, are both white suspensions and have a matching appearance.

DTaP, HBV, IPV, and Hib vaccine, Infanrix hexa (supplied as a vial and a prefilled syringe), is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, hepatitis B caused by all known subtypes of hepatitis B virus, poliomyelitis, and Hib infection, respectively. See the investigational product manual (IP manual) and applicable SRSD.

MMR vaccine (supplied as a vial and prefilled syringe with solvent) is a live virus vaccine for vaccination against measles (rubeola), mumps, and rubella (German measles). See the IP manual and applicable SRSD provided.

Varicella vaccine (supplied as a vial and prefilled syringe with solvent) is a live virus vaccine for vaccination against varicella. See the IP manual and applicable SRSD.

Investigational product will be supplied by Pfizer as prefilled syringes or vials. Each syringe/vial will be packaged in a carton with a label and a tamper-evident seal, and will be labeled as required per country requirement (refer to the IP manual).

6.1.1. Administration

Participants will receive 1 dose of 20vPnC or 13vPnC at each vaccination visit (Visits 1, 2, and 4) in accordance with the study's SoA.

Participants will also receive 1 dose of DTaP, HBV, IPV, and Hib vaccine at Visits 1, 2, and 4. Participants are also to receive MMR and varicella vaccines at Visit 4 in accordance with the study's SoA. The MMR and varicella vaccines are intended to be given to all participants. However, in case of circumstances due to local practice/recommendations, some sites may not administer them to their participants at Dose 3, in which case MMR and varicella vaccines will be considered nonstudy vaccines. If MMR and varicella vaccines are not given with Dose 3, and administered based on local practice/recommendations, they are not to be given during the interval <28 days before Dose 3 through the Visit 5 blood draw after Dose 3.

20vPnC and 13vPnC should be administered intramuscularly by injecting 0.5 mL into the anterolateral thigh muscle of the left leg at the vaccination visits.

The DTaP, HBV, IPV, and Hib vaccine will be administered concomitantly with 20vPnC or 13vPnC and must be given in a limb other than the site of administration of 20vPnC or 13vPnC, as appropriate for the age of the child and the route of administration (ie, intramuscular or subcutaneous).

The MMR and varicella vaccines will be administered concomitantly with 20vPnC or 13vPnC and must be given in a limb other than the site of administration of 20vPnC or 13vPnC, as appropriate for the age of the child and the route of administration (ie, intramuscular or subcutaneous).

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

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

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

6.1.2. Medical Devices

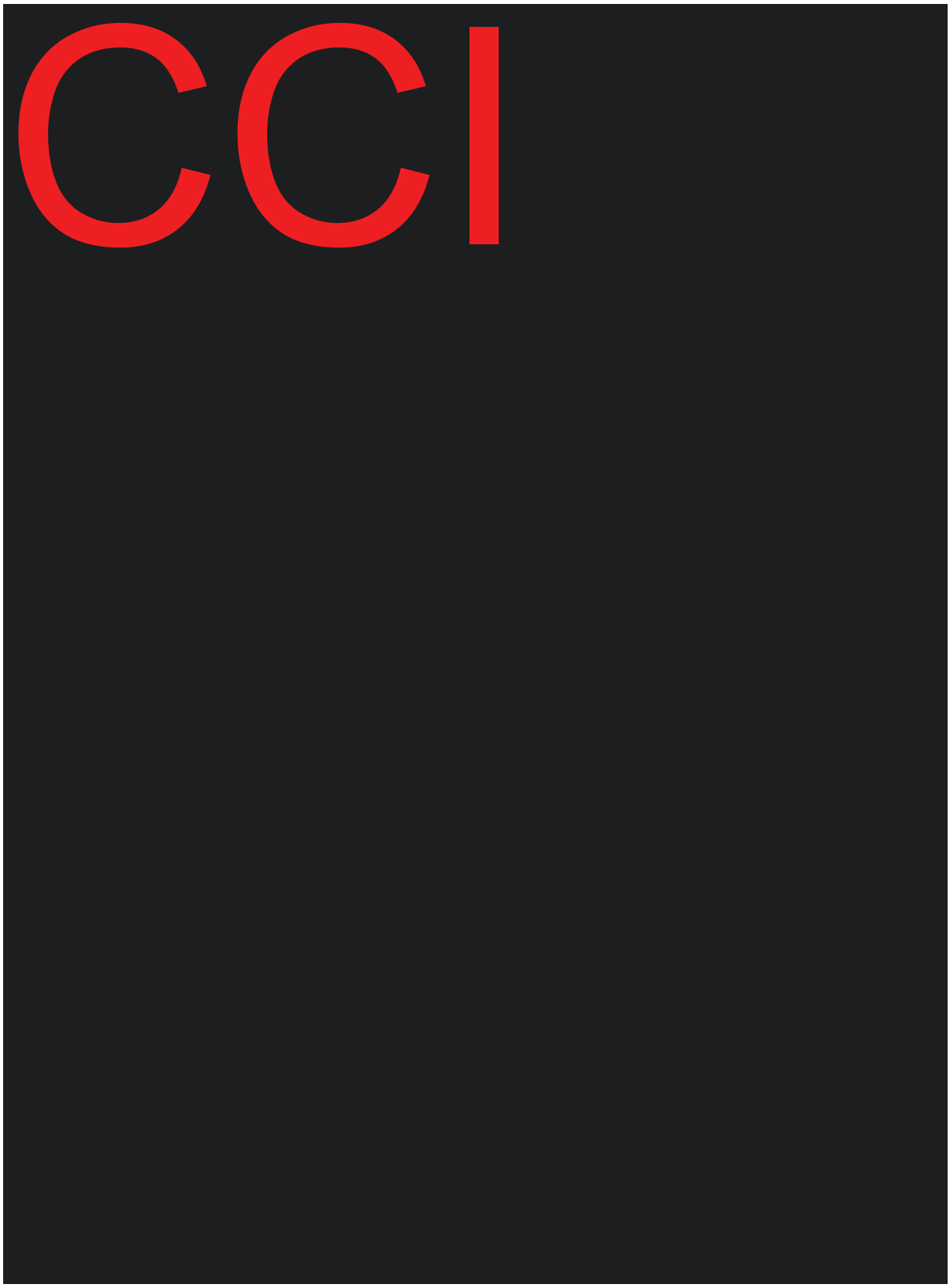
In this study, medical devices being deployed are the 20vPnC and 13vPnC, DTaP, HBV vaccine, IPV, and Hib vaccine prefilled syringes, and the MMR and varicella vaccine prefilled syringes.

Instructions for medical device use are provided in the IP manual or in the package insert.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the study personnel throughout the study. Please refer to Section 8.3.7 for details.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.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Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual or package insert for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

All eligible participants will be randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine).

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

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

6.3.2. Blinding of Sponsor

Sponsor personnel involved in evaluating participant data in the primary study population will be blinded to vaccine assignment until the final analysis at the completion of participation of the primary study population, following the principles outlined in International Council for Harmonisation (ICH) E9 guideline on Statistical Principles for Clinical Trials.[73] The study team will remain blinded to the vaccine assignments of the Russian cohort until that cohort has completed the study. A data blinding plan will be created to describe the blinding requirements and unblinding events. Laboratory personnel

performing the immunologic assays will be blinded until all assays have been completed and assay results finalized.

6.3.3. Breaking the Blind

The study will be participant- and investigator-blinded.

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

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

6.5.1. Prohibited Concomitant Vaccines and Treatments

- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during study participation.
- Receipt of nonstudy pneumococcal vaccine is prohibited during study participation.
- No additional doses of the study concomitant vaccines are allowed during the study except as prescribed by the protocol (eg, only 2 infant and 1 toddler dose of Infanrix hexa can be given, and should be given consistent with the protocol).
- Receipt of blood/plasma products, immunoglobulins, and/or immunosuppressive therapy (including a ≥14-day course of systemic corticosteroids) is prohibited during study participation.

6.5.2. Permitted Concomitant Vaccines and Treatments

- Licensed inactivated influenza vaccine may be given at any time during the study per national recommendations.
- Rotavirus vaccine may be given at any time during the study, and according to local or national recommendations.
- Meningitis B vaccine may be given during the study as per national recommendations. It must be given at least 2 weeks before and/or 2 weeks after scheduled study vaccinations, and in accordance with local recommendations.

- Receipt of meningococcal conjugate vaccines is permitted after the blood draw at Visit 5.
- Receipt of other licensed nonstudy vaccines is permitted after the Visit 5 blood draw.
- Use of topical anesthetic is permitted during the study per local practice.
- The use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.
- Inhaled/nebulized, topical (skin, eyes, or ears), or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted during participant participation in the study.
- Prescription and nonprescription medications, vitamins, minerals, and herbal remedies are permitted during the study.

6.5.3. Prior Vaccines and Treatments

- A birth dose of bacille Calmette-Guérin (BCG) vaccine may be given at least 28 days before vaccination with the first dose of investigational product.
- Receipt of hepatitis B vaccine at birth is permitted but must be at least 28 days before the first vaccination of investigational product.

6.5.4. Recording Prior and Concomitant Vaccines and Treatments

The name and date of administration for all vaccinations should be collected from the time of signing of the ICD to Visit 5 and will be recorded in the CRF. At Visit 1, information on prior vaccinations will also be recorded in the CRF. Vaccines required by the protocol, as well as those not stipulated, will be recorded throughout study participation. Information on vaccines given to the mother during pregnancy and any intrapartum antibiotic use will also be collected (at Visit 1 only), if available.

Medications taken to treat SAEs and NDCMCs from the signing of the ICD to the final visit (Visit 5) will be recorded on the CRF.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participant eligibility must be confirmed prior to each vaccination in order to continue in the study.

If a participant no longer meets the eligibility criteria during the vaccination period of the study, further vaccinations should be discontinued, but the participant may remain in the study. If a participant is discontinued from vaccination and the participant's parent(s)/legal guardian(s) consents, safety follow-up will be conducted as per Section 8.3. AEs, SAEs, and NDCMCs will be collected for 1 month after the last study vaccination.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may be withdrawn from the study at any time at the request of his/her parent(s)/legal guardian(s), or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant's parent(s)/legal guardian(s). All attempts to contact the participant's parent(s)/legal guardian(s) and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

At the time of discontinuing from the study, please refer to the investigator site file (ISF) and SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant's parent(s)/legal guardian(s) should ideally notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The participant's parent(s)/legal guardian(s) should be questioned regarding their reason for withdrawal. The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

The participant should be requested to return for a final visit, if applicable, and the investigator will perform the procedures indicated for the next visit. Any AEs or SAEs that are continuing at the time of withdrawal from the study should be followed until resolution or, in case of permanent impairment, until the condition stabilizes.

The collection of safety information should be completed for all participants who have been withdrawn after administration of investigational product, unless consent for further contact has been withdrawn, or the participant is lost to follow-up.

Participant withdrawal should be explained in the source documents and should include whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up. The participant will be monitored for AEs, SAEs, and NDCMCs for 1 month after the last study vaccination.

If a participant is withdrawn from the study, his/her parent(s)/legal guardian(s) may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant is withdrawn from the study and his/her parent(s)/legal guardian(s) also withdraws consent (see below) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant is withdrawn from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Vaccine SAE Reporting Form.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and the participant's parent(s)/legal guardian(s) is unable to be contacted by the study site.

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

- The site must attempt to contact the participant's parent(s)/legal guardian(s) and reschedule the missed visit as soon as possible and counsel the participant's parent(s)/legal guardian(s) on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant's parent(s)/legal guardian(s) wishes for the participant to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant's parent(s)/legal guardian(s) (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant's parent(s)/legal guardian(s) continue to be unreachable, the participant will be considered to have been withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

In the case of extreme circumstances, such as natural disasters or a pandemic, visits for follow-up or procedures may need to be conducted through other means (eg, telephone calls).

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

The total blood sampling volume for individual participants in this study is approximately 15 to 25 mL,CCI

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8.1. Efficacy Assessments

8.1.1. Immunogenicity Assessments

Blood samples (approximately 5 mL per sample) will be collected from all participants at Visits 3 (1 month after Dose 2), 4 (prior to Dose 3), and 5 (1 month after Dose 3). These are

the immunogenicity time points. OPA titers will be determined for a randomly selected subset of participants.

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Pneumococcal Responses

IgG Responses to the 20 Serotypes Contained in 20vPnC

IgG antibody concentrations for serotypes present in 20vPnC (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) will be determined on all sera collected at the 5 immunogenicity time points (prior to Dose 1, prior to Dose 2, 1 month after Dose 2, prior to Dose 3, and 1 month after Dose 3). The serotype-specific IgG concentrations will be measured by Pfizer's multiplex Luminex immunoassay.

OPA Responses to the 20 Serotypes Contained in 20vPnC

OPA titers for serotypes present in 20vPnC (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) will be determined in subsets of sera for the 3 key immunogenicity time points (1 month after Dose 2, prior to Dose 3, and 1 month after Dose 3) in a randomly selected subset of the study participants. These subsets will be randomly selected, by an unblinded third party, to ensure that each subset has equal representation of both vaccine groups. Further details will be described in the clinical specimen assessment plan (CSAP).

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Concomitant Vaccine Antigens

Concomitant vaccine responses to the following antigens will be assessed. The randomly selected serum subsets to be assayed will be based on minimum sample sizes needed to demonstrate the objectives of the study balanced with the serum volume required and available for testing. These subsets will be randomly selected, by an unblinded third party, to ensure that each subset has equal representation of both vaccine groups. Further details will be described in the CSAP. The serum subsets for MMR and varicella response will be randomly selected from participants who receive MMR and varicella vaccines at Dose 3.

Diphtheria toxoid: Concentration of antibody (in international units [IU]) to diphtheria toxoid (prespecified level ≥0.1 IU/mL) will be determined on the subsets of sera collected at the 2 immunogenicity time points (1 month after Dose 2 and 1 month after Dose 3). CCI
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Tetanus toxoid: Concentration of antibody (in IU) to tetanus toxoid (prespecified level ≥0.1 IU/mL) will be determined on the subsets of sera collected at the 2 immunogenicity time points (1 month after Dose 2 and 1 month after Dose 3). CCI CCI

Acellular pertussis: Concentration of IgG antibodies to pertussis antigens PT, FHA, and PRN (prespecified level ≥ the observed antipertussis antibody concentration achieved by 95% of 13vPnC recipients) will be determined on the subsets of sera collected at the 2 immunogenicity time points (1 month after Dose 2 and 1 month after Dose 3). CCI CCI

Hepatitis B: Concentration of hepatitis B antibody (in milli-international units per mL [mIU/mL]) (prespecified level ≥10 mIU/mL) will be determined on the subsets of sera collected at 1 immunogenicity time point (1 month after Dose 3). CCI CCI

Poliomyelitis: Neutralizing antibody (NA) titers to poliovirus types 1, 2, and 3 (prespecified level NA titer ≥1:8) will be determined on the subsets of sera collected at the 2 immunogenicity time points (1 month after Dose 2 and 1 month after Dose 3). CCI CCI

Hib: Concentration of antibody to Hib (polyribosylribitol phosphate [PRP]) in µg/mL (prespecified level ≥0.15 µg/mL anti-PRP; alternative prespecified level ≥1.0 µg/mL anti-PRP) will be determined on the subsets of sera collected at the 2 immunogenicity time points (1 month after Dose 2 and 1 month after Dose 3). CCI CCI

Measles: Concentration of antimeasles antibody will be determined on the subsets of sera collected at 1 immunogenicity time point (1 month after Dose 3). CCI CCI

Mumps: Concentration of antimumps antibody will be determined on the subsets of sera collected at 1 immunogenicity time point (1 month after Dose 3). CCI CCI

Rubella: Concentration of antirubella antibody will be determined on the subsets of sera collected at 1 immunogenicity time point (1 month after Dose 3). CCI CCI

Varicella: Concentration of antivaricella antibody will be determined on the subsets of sera collected at 1 immunogenicity time point (1 month after Dose 3). CCI CCI

For Russian cohort–specific differences, please see Section 10.10.1.

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8.1.2. 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 participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. CCI

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CCI No testing of the participant's genetic material will be performed.

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

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

A clinical assessment, including medical history and measurement of temperature, will be performed on all participants prior to vaccination to determine participant eligibility and to establish a clinical baseline. Significant medical history and significant findings from any physical examination (if performed) will be recorded as medical history on the CRF. Temperature measurement prior to vaccination will be documented and recorded on the CRF.

The participant will be observed for 30 minutes after each study vaccination and any reactions occurring during that time will be recorded as AEs.

Local reactions (including redness, pain, and swelling at the injection site), systemic events (including fever, drowsiness/increased sleep, decreased appetite, and irritability), and use of pain/fever medication will be prompted for and collected by the participant's parent(s)/legal guardian(s) daily for 7 days after each study vaccination (where Day 1 is the day of vaccination) in an e-diary. These prompted e-diary events are graded as described in Section 8.2. AEs, SAEs, and NDCMCs will be collected as defined in Section 8.3.

AEs will be recorded and reported from the signing of the ICD through Visit 3 and from Visit 4 through Visit 5.

SAEs and NDCMCs will be recorded and reported from the signing of the ICD through the final visit (Visit 5).

Causality and severity of AEs and SAEs will be assessed for all participants.

8.2.1. Participant Electronic Diary

The participant's parent(s)/legal guardian(s) will be asked to monitor and record local reactions, specific systemic events, and antipyretic/pain medication taken for 7 days, each evening, following each vaccination using an e-diary (in a provisioned device or application on a personal device). This allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience. Data on local reactions, specific systemic events, and antipyretic/pain medication reported in 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.

The daily e-diary data will not be captured in the CRF. However, if a participant withdraws because of prompted events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

The investigator or designee must obtain stop dates for any reactions ongoing on the last day that the e-diary was completed. The stop dates should be entered in the CRF.

Designated site staff will review the e-diary data online at frequent intervals (daily is optimal) for the 7 days following each dose of 20vPnC or 13vPnC to evaluate participant compliance and reported events as part of the ongoing safety review.

8.2.2. Grading Scale for Prompted Events

The grading scales used in this study to assess prompted events 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 adults and adolescent volunteers enrolled in preventive vaccine clinical trials, but have been adapted for applicability to healthy infants.[74]

8.2.2.1. Local Reactions

For the first 7 days following each vaccination (Days 1 through Day 7, where Day 1 is the day of vaccination), the participant's parent(s)/legal guardian(s) will be asked to assess redness, swelling, and pain at the 20vPnC or 13vPnC 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 (caliper) units (range: 1 to >14; an entry in the e-diary of 15

will denote >14), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the participant's parent(s)/legal guardian(s) as mild, moderate, or severe according to the grading scale in Table 1. The participant's parent(s)/legal guardian(s) will be prompted to contact the investigator if the participant experiences a severe (Grade 3) or above local reaction to assess the reaction and perform an unscheduled assessment or visit as appropriate.

Only an investigator is able to classify a participant's local reaction as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the participant's parent(s)/legal guardian(s) regarding signs and symptoms that would prompt site contact.

The procedure for notification of the sponsor is provided in the study reference manual (SRM) or equivalent.

Table 1. Grading Scales for Local Reactions

Local Reaction	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3[a] Severe	GRADE 4[b]
Redness	1 to 4 caliper units (or measuring device units) = >0 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis or exfoliative dermatitis
Swelling	1 to 4 caliper units (or measuring device units) = >0 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis
Pain at injection site (tenderness)	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched with crying	Causes limitation of limb movement	Emergency room visit or hospitalization for severe pain (tenderness) at injection site

Abbreviations: CRF = case report form; e-diary = electronic diary.

a. Parent(s)/legal guardian(s) of the participants experiencing local reactions >14 caliper units (>7.0 cm) are to be contacted by the study site. An unscheduled visit may be required.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF (see Section 10.3.4).

Note: If the size of the redness and/or swelling falls between 2 measuring device units, the higher measuring device unit number will be recorded in the e-diary.

8.2.2.2. Systemic Event Symptoms and Fever

8.2.2.2.1. Systemic Event Symptoms

For the first 7 days following each vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination), the participant's parent(s)/legal guardian(s) will be asked to assess decreased appetite, drowsiness/increased sleep, and irritability and to record the symptoms in the e-diary (in a provisioned device or application on a personal device) in the evening. The symptoms will be assessed by the participant's parent(s)/legal guardian(s) as mild, moderate, or severe according to the grading scale in Table 2. The participant's parent(s)/legal guardian(s) will also be instructed to contact site staff if the participant experiences any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for severe decreased appetite, severe drowsiness/increased sleep, or severe irritability) within 7 days after vaccination. Study staff may also contact the participant's parent(s)/legal guardian(s) to obtain additional information on Grade 3 events entered into the e-diary.

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

The procedure for notification of the sponsor is provided in the SRM or equivalent.

Table 2. Grading Scales for Systemic Event Symptoms

Systemic Event	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4[a]
Decreased appetite (loss of appetite)	Decreased interest in eating	Decreased oral intake	Refusal to feed	Emergency room visit or hospitalization for severe decreased appetite (loss of appetite)
Drowsiness (increased sleep)	Increased or prolonged sleeping bouts	Slightly subdued interfering with daily activity	Disabling not interested in usual daily activity	Emergency room visit or hospitalization for severe drowsiness (increased sleep)
Irritability (fussiness) (synonymous with restless sleep; decreased sleep)	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted	Emergency room visit or hospitalization for severe irritability (fussiness)

Abbreviations: CRF = case report form; e-diary = electronic diary.

a. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF (see Section 10.3.4).

8.2.2.2.2. Fever

In order to record information on fever, a digital thermometer will be given to the participant's parent(s)/legal guardian(s) with instructions on how to measure axillary temperature at home. Temperature will be collected in the evening, daily, for 7 days following vaccination (Days 1 to 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an axillary temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on the last day of diary collection, temperature will be collected daily until fever has resolved (1 day of temperature less than 38.0°C [100.4°F]) in order to collect a stop date in the CRF. A participant's parent(s)/legal guardian(s) will be prompted to contact the investigator if the participant experiences a fever >40.0°C (>104.0°F) within the 7 days following vaccination to assess the fever and perform an unscheduled assessment, as applicable (see Section 8.10.6). Study staff may also contact the participant's parent(s)/legal guardian(s) to obtain additional information if a temperature of >38.9°C (>102.0°F) is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis; see Table 3.

Table 3. Ranges for Fever

≥38.0°C to 38.4°C
>38.4°C to 38.9°C
>38.9°C to 40.0°C
>40.0°C

Note: Fever is defined as temperature ≥38.0°C.

8.2.2.3. Use of Antipyretic/Pain Medication

The participant's parent(s)/legal guardian(s) will be asked to record the use of antipyretic/pain medication (yes/no) in the e-diary (in a provisioned device or application on a personal device) in the evening, daily, for 7 days after each dose of investigational product.

The use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.

8.2.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory tests are not required by this protocol.

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant's parent(s)/legal guardian(s). Events that, in the clinical judgment of the investigator, are 1) consistent with normal growth and development and 2) do not differ significantly in frequency or severity from expected are not generally to be considered AEs. Examples may include, but are not limited to, teething, contact diaper rash, spitting up, colic, or typical fussiness/crying in infants and children.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or caused the participant to discontinue from the study (see Section 7).

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

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant's parent(s)/legal guardian(s) provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 3, and from Visit 4 through Visit 5. SAEs and NDCMCs will be recorded and reported from the signing of the ICD through the final visit (Visit 5). At Visit 5, the participant's parent(s)/legal guardian(s) will be asked to report any AEs and SAEs, including hospitalizations and NDCMCs, that have occurred since Visit 4.

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant's parent(s)/legal guardian(s) is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in females (via occupational exposure) will be collected after the start of study intervention and until delivery.

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

8.3.5.2. Exposure During Breastfeeding

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Adverse Events of Special Interest

Not applicable.

8.3.6.1. Lack of Efficacy

This section is not applicable because efficacy is not expected to be detected (vaccine is expected to be efficacious) in the study population.

8.3.7. Medical Device Deficiencies

Medical devices are being provided for use in this study for the purposes of administering the investigational product. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 8.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

8.3.7.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 8.

8.3.7.2. Follow-up of Medical Device Deficiencies

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). This applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the follow-up form with all changes signed and dated by the investigator.

8.3.7.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP manual.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Section 8.3.1.1 and Section 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.7.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.8. Medication Errors

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

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

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

Medication errors include:

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

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 within 24 hours.

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

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

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.

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than 0.5 mL within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

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

8.10. Study Procedures

The study procedures are summarized in the SoA. The day of Dose 1 is considered to be Day 1. The timing of visit procedures (ie, prior to vaccination and after vaccination) must be maintained; however, there is flexibility in the order in which the procedures can be conducted at each visit. The only exception is that at Visit 1, the ICD must be signed prior to the start of any study procedure.

8.10.1. Visit 1 (Dose 1: Day 1)

Prior to vaccination:

- Obtain a personally signed and dated ICD indicating the participant's parent(s)/legal guardian(s) has been informed of all pertinent aspects of the study before performing any study-specific procedures.
- Assign a participant number via the IRT.
- Obtain and record the participant's demographic information (including date of birth, sex, race, and ethnicity). The complete date of birth (ie, DD-MMM-YYYY) will be collected to critically evaluate the immune response and safety profile by age.
- Perform a clinical assessment that includes medical history, including significant birth history; record any findings on the medical history CRF.
- Record vaccination history.
- Record vaccines administered during pregnancy and intrapartumn antibiotic use (yes/no) (if available).
- Measure and record the participant's temperature (°C) as appropriate for age.
- Ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- Assign a randomization number and an investigational product container number via the IRT. This must be the last step before proceeding. A site staff member will prepare the investigational product according to the IP manual.

After randomization:

[redacted]

- Administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh.

- Administer concomitant vaccine containing DTaP, HBV, IPV, and Hib antigens and other permitted vaccines (must be given in a limb other than the site of 20vPnC or 13vPnC administration, as appropriate for the age of the child and the route of administration [ie, intramuscular, subcutaneous, or oral]). The site of administration will be captured on the CRF.

- Site staff will observe the participant for 30 minutes after vaccination for any reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs and NDCMCs.

- Issue the participant's parent(s)/legal guardian(s) a measuring device to measure 20vPnC or 13vPnC injection site reactions and a digital thermometer and provide instructions on their use.

- Issue the participant's parent(s)/legal guardian(s) an e-diary (device or application). Provide instructions on use and completion of the e-diary. Ask the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C (>104.0°F), redness and/or swelling at the 20vPnC or 13vPnC injection site measuring >14 measuring device units (>7 cm), or severe 20vPnC or 13vPnC injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Ask the participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.

- Provide the parent(s)/legal guardian(s) with the participant contact card containing the study and investigator information (see Section 10.1.10).

- Inform the participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.

- The investigator or an authorized designee completes the CRFs and updates the investigation product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of ongoing safety review.

8.10.2. Visit 2 (Dose 2: 42 to 63 Days After Visit 1, ie, Study Day 43 Through Study Day 64)

- Ensure and document that the participant continues to be eligible for the study (see Section 7 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Confirm whether the parent(s)/legal guardian(s) still possesses the participant contact card.

- Record nonstudy vaccinations administered since Visit 1, as described in Section 6.5.4.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); collect stop dates of any local and systemic events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3.4, and record concomitant medications used to treat NDCMCs and SAEs.

- Measure and record the participant's temperature (°C).

[redacted]

- Administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh.

- Administer concomitant vaccine containing DTaP, HBV, IPV, and Hib antigens and other permitted vaccines (must be given in a limb other than the site of 20vPnC or 13vPnC administration, as appropriate for the age of the child and the route of administration [ie, intramuscular, subcutaneous, or oral]). The site of administration will be captured on the CRF.

After vaccination:

- Site staff will observe the participant for 30 minutes after vaccination for any reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs and NDCMCs.

- Confirm that the e-diary is working and review instructions if necessary. Remind the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination. Provide a digital thermometer or measuring device if needed.

- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C (>104.0°F), redness and/or swelling at the 20vPnC or 13vPnC injection site measuring >14 measuring device units (>7 cm), or severe 20vPnC or 13vPnC injection site pain (causes limitation of limb movement), to determine if the event requires further assessment by the investigator.

- Remind the participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.

- Remind the participant's parent(s)/legal guardian(s) that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.

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

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of ongoing safety review.

8.10.3. Visit 3 (Dose 2 Follow-up: 28 to 42 Days After Visit 2)

- Ensure and document that the participant continues to be eligible for the study (see Section 7 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Confirm whether the parent(s)/legal guardian(s) still possesses the participant contact card.

- Record nonstudy vaccinations administered since Visit 2, as described in Section 6.5.4.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); collect stop dates of any local and systemic events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Collect the e-diary (if applicable).

- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3.4, and record concomitant medications used to treat NDCMCs and SAEs.

- Collect a blood sample of approximately 5 mL for immunogenicity (a topical anesthetic is permitted).

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

8.10.4. Visit 4 (Dose 3: 335 to 386 Days of Age)

- Ensure and document that the participant continues to be eligible for the study (see Section 7 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Confirm whether the parent(s)/legal guardian(s) still possesses the participant contact card.

- Record nonstudy vaccinations administered since Visit 3, as described in Section 6.5.4.

- Determine whether any SAEs or NDCMCs have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3.4, and record concomitant medications used to treat NDCMCs and SAEs. Any AEs that have occurred since the last visit will be documented in the participant's source documents; however, they will not be captured on the CRF.

- Measure and record the participant's temperature (°C).

- Collect a blood sample of approximately 5 mL for immunogenicity (a topical anesthetic is permitted).

- Administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh.

- Administer concomitant vaccine containing DTaP, HBV, IPV, and Hib antigens and other permitted vaccines. These vaccines must be given in a limb other than the site of

20vPnC or 13vPnC administration, as appropriate for the age of the child and the route of administration (ie, intramuscular, subcutaneous, or oral). The sites of administration will be captured on the CRF.

- MMR and varicella vaccines are intended to be given to all participants. However, in case of circumstances due to local practice/recommendations, some sites may not administer them to their participants, in which case MMR and varicella vaccines will be considered nonstudy vaccines. These vaccinations must be given in a limb other than the site of administration of 20vPnC or 13vPnC, as appropriate for the age of the child and the route of administration (ie, intramuscular or subcutaneous). The sites of administration will be captured on the CRF.

After vaccination:

- Site staff will observe the participant for 30 minutes after vaccination for any reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs and NDCMCs.

- Reissue the participant's parent(s)/legal guardian(s) an e-diary (device or application). Provide instructions on use and completion of the e-diary. Ask the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C (>104.0°F), redness and/or swelling at the 20vPnC or 13vPnC injection site measuring >14 measuring device units (>7 cm), or severe 20vPnC or 13vPnC injection site pain (causes limitation of limb movement), to determine if the event requires further assessment by the investigator.

- Remind the participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.

- Remind the participant's parent(s)/legal guardian(s) that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.

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

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of ongoing safety review.

8.10.5. Visit 5 (Dose 3 Follow-up: 28 to 42 Days After Visit 4)

- Ensure and document that the participant continues to be eligible for the study (see Section 7 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).
- Record nonstudy vaccinations administered since Visit 4, as described in Section 6.5.4.
- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); collect stop dates of any local and systemic events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Collect the e-diary (if applicable).
- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3.4, and record concomitant medications used to treat NDCMCs and SAEs.
- Collect a blood sample of approximately 5 mL for immunogenicity (a topical anesthetic is permitted).
- The investigator or an authorized designee completes the CRF and the source documents and updates the investigational product accountability records.

8.10.6. Unscheduled Visits

If the participant's parent(s)/legal guardian(s) reports redness or swelling at the injection site measuring >14 measuring device units (>7 cm), severe injection site pain, or a fever >40.0°C (>104.0°F) during the 7-day postvaccination period, a telephone contact must occur as soon as possible between the investigator or medically qualified designee and the participant's parent(s)/legal guardian(s) to assess if an unscheduled investigator site visit is required. Note that for a fever >40.0°C (>104.0°F), the participant's parent(s)/legal guardian(s) should be instructed not to delay seeking medical care, as appropriate, while arranging for an unscheduled visit, if applicable. A visit should be scheduled as soon as possible to assess the extent of the injection site reaction, unless any of the following is true:

- The participant's parent(s)/legal guardian(s) is unable to bring the participant to the unscheduled visit.
- The reaction is no longer present at the time of the telephone contact.
- The participant's parent(s)/legal guardian(s) recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The investigator or authorized designee determined it was not needed.

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

If the participant's parent(s)/legal guardian(s) is unable to bring the participant to an unscheduled visit, or the principal investigator or authorized designee determined it was not needed, any ongoing reactions must be assessed at the next study visit.

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

- Measure temperature (°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain in accordance with the grades provided in Section 8.2.2 (if present).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

The participant's parent(s)/legal guardian(s) will also be instructed to contact investigator site staff if the participant experiences any emergency room visit or hospitalization for decreased appetite, drowsiness/increased sleep, irritability, or local reaction within 7 days of vaccination.

The participant's parent(s)/legal guardian(s) will also be instructed to contact the investigator site to report any significant illness, medical event, or hospitalization that occurs during the study period. The investigator site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

Additionally, study staff may contact the participant's parent(s)/legal guardian(s) to obtain additional information on Grade 3 events entered into the e-diary.

For specific modifications of visit windows, blood sample collection, and concomitant vaccine administration in the Russian cohort, please see Sections 10.10.1 and 10.10.2.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where

appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimands corresponding to each objective are described in the table in Section 3. The estimands to evaluate the immunogenicity objectives for NI are based on evaluable populations (see Section 9.3 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. The estimand addresses the objective of estimating the maximum potential difference between 2 groups, since the impact of noncompliance is likely to diminish the observed difference between the 2 groups. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The endpoints and estimands corresponding to the objectives for the Russian cohort can be found in Section 10.10.3. All the statistical analysis for the Russian cohort will be descriptive.

9.1.2. Statistical Hypotheses

All hypothesis testing will be performed on the data from the primary study population.

9.1.2.1. Pneumococcal Immunogenicity Hypotheses

9.1.2.1.1. Percentage of Participants With Predefined Pneumococcal Serotype-Specific IgG Concentrations 1 Month After Dose 2

Hypothesis testing will be used to assess the NI of 20vPnC to 13vPnC for the percentage of participants with predefined pneumococcal serotype-specific IgG concentrations 1 month after Dose 2. The null hypothesis (H_{0A}) for a serotype is

$$H_{0A}: \pi_{20vPnC} - \pi_{13vPnC} \leq -10\%,$$

with a 10% margin for NI, where

- π_{20vPnC} is the percentage of participants achieving an IgG antibody concentration of predefined level in the 20vPnC group for the serotype 1 month after Dose 2;
- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) in 13vPnC, π_{13vPnC} is the percentage of participants achieving a predefined IgG concentration for the serotype from the 13vPnC group 1 month after Dose 2;

- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, π_{13vPnC} is the percentage of participants achieving a predefined IgG concentration from the serotype with the lowest percentage among the 13 serotypes from the 13vPnC group 1 month after Dose 2, provided that the lowest percentage is not from serotype 3. If the lowest percentage in the 13vPnC group is from serotype 3, the next lowest percentage in the 13vPnC group will be used in the comparison. Historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the NI of the 7 additional serotypes;

- The predefined levels for serotype-specific IgG concentrations are 0.35 µg/mL for all serotypes in 20vPnC except that the predefined levels are 0.23 µg/mL, 0.10 µg/mL, and 0.12 µg/mL for serotypes 5, 6B, and 19A, respectively.

The null hypothesis (H_{0A}) will be rejected and NI of 20vPnC to 13vPnC for the percentage of participants with predefined IgG concentration for a serotype will be declared if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages, computed using the Miettinen and Nurminen method, is greater than –10% (10% NI margin).

9.1.2.1.2. Pneumococcal Serotype-Specific IgG GMCs 1 Month After Dose 2

Hypothesis testing will be used to assess the NI of 20vPnC to 13vPnC for pneumococcal serotype-specific IgG GMCs 1 month after Dose 2. The null hypothesis (H_{0B}) for a serotype is

$$H_{0B}: \ln(\mu_{20vPnC}) - \ln(\mu_{13vPnC}) \leq \ln(0.5)$$

where ln(0.5) corresponds to a 2-fold margin for NI and

- $\ln(\mu_{20vPnC})$ is the natural log of the geometric mean IgG concentration in the 20vPnC group for that serotype 1 month after Dose 2;

- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration in the 13vPnC group 1 month after Dose 2;

- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration for the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group 1 month after Dose 2, provided that the lowest GMC is not from serotype 3. If the lowest GMC in the 13vPnC group is from serotype 3, the next lowest GMC in the 13vPnC group will be used in the comparison. As stated in Section 9.1.2.1.1, historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the NI of the 7 additional serotypes.

The null hypothesis (H_{0B}) will be rejected and NI of 20vPnC to 13vPnC for the pneumococcal serotype-specific IgG GMC will be declared for a serotype if the lower bound of the 2-sided 95% CI for the IgG GMR of 20vPnC to 13vPnC is greater than 0.5 (2-fold NI margin).

9.1.2.1.3. Pneumococcal Serotype-Specific IgG GMCs 1 Month After Dose 3

Hypothesis testing to assess the NI of 20vPnC to 13vPnC for pneumococcal serotype-specific IgG GMCs 1 month after Dose 3 will be performed similarly to that for IgG GMCs 1 month after Dose 2, as described in Section 9.1.2.1.2, with $\ln(\mu_{20vPnC})$ and $\ln(\mu_{13vPnC})$ being the natural log of the geometric mean IgG concentrations 1 month after Dose 3 from the 20vPnC and 13vPnC groups, respectively, except for the 7 additional serotypes in 20vPnC, where $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration for the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group, provided that the lowest GMC is not from serotype 3. If the lowest GMC in the 13vPnC group is from serotype 3, the next lowest GMC in the 13vPnC group will be used in the hypothesis testing.

The null hypothesis (H_{0C}: $\ln[\mu_{20vPnC}] - \ln[\mu_{13vPnC}] \leq \ln[0.5]$) will be rejected and NI of 20vPnC to 13vPnC for the pneumococcal serotype-specific IgG GMC will be declared for a serotype if the lower bound of the 2-sided 95% CI for the IgG GMR of 20vPnC to 13vPnC for the serotype is greater than 0.5 (2-fold NI margin).

9.1.2.2. Concomitant Immunogenicity Hypotheses

9.1.2.2.1. Noninferiority for Percentage of Participants With a Prespecified Antibody Level to Each Concomitant Vaccine Antigen 1 Month After Dose 3

Hypothesis testing will be used to assess the NI of the 20vPnC group to the 13vPnC group for the percentage of participants with a prespecified antibody level to each concomitant vaccine antigen at 1 month after Dose 3. The null hypothesis (H_{0C}) for each concomitant vaccine antigen is

$$H_{0C}: \pi_{20vPnC} - \pi_{13vPnC} \leq -10\%$$

with a 10% margin for NI, where π_{20vPnC} and π_{13vPnC} are the percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, or Hib at 1 month after Dose 3, from the 20vPnC group and the 13vPnC group, respectively.

The following are the prespecified antibody thresholds for the concomitant vaccine antigens:

Antigen	Prespecified Level
Diphtheria	≥0.1 IU/mL
Tetanus	≥0.1 IU/mL
Acellular pertussis (PT, FHA, PRN)	≥ the observed antipertussis antibody concentration achieved by 95% of 13vPnC recipients

Antigen	Prespecified Level
Hepatitis B	≥10 mIU/mL
Poliomyelitis (types 1, 2 and 3)	≥1:8
Hib	≥0.15 µg/mL anti-PRP Alternative: ≥1.0 µg/mL anti-PRP

The null hypothesis (H_{0C}) testing for NI will be rejected for a concomitant vaccine antigen if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages, computed using the Miettinen and Nurminen method, is greater than –10% (10% NI margin).

9.1.2.2.2. Noninferiority for GMCs of Antibody Levels to Concomitant Vaccine Antigens 1 Month After Dose 3

Hypothesis testing will be used to assess the NI of the 20vPnC group to the 13vPnC group for GMCs of antibody levels to each concomitant vaccine antigen 1 month after Dose 3. The null hypothesis (H_{0D}) for each concomitant vaccine antigen is

$$H_{0D}: \ln(\mu_{20vPnC}) - \ln(\mu_{13vPnC}) \leq \ln(0.5)$$

where ln(0.5) corresponds to a 2-fold margin for NI, and $\ln(\mu_{20vPnC})$ and $\ln(\mu_{13vPnC})$ are the natural log of the GMCs for antibody levels to measles, mumps, rubella, and varicella virus at 1 month after Dose 3 from the 20vPnC group and the 13vPnC group, respectively.

The null hypothesis (H_{0D}) testing for NI will be rejected for a concomitant vaccine antigen if the lower bound of the 2-sided 95% CI for the GMR of GMCs (20vPnC over 13vPnC) is greater than 0.5 (2-fold NI margin).

9.1.3. Multiplicity Consideration

Primary Pneumococcal Immunogenicity Evaluation

For the primary pneumococcal immunogenicity objectives comparing serotype-specific IgG concentrations from the 20vPnC group to that from the 13vPnC group, NI of the immune response for each serotype is assessed by the hypothesis tests as described in Section 9.1.2.1.1 and Section 9.1.2.1.2, each at an alpha level of 0.05. The primary pneumococcal immunogenicity objectives will be achieved if NI of the immune response induced by 20vPnC compared to 13vPnC based on both percentages of participants with predefined IgG levels and IgG GMCs at 1 month after Dose 2, as well as the IgG GMCs at 1 month after Dose 3, is established for all 20 serotypes, a total of 60 NI evaluations. Therefore, the overall type I error rate for the primary immunogenicity assessment of the pneumococcal immune response of 20vPnC 1 month after Dose 3 is well controlled at the 0.05 level.

Primary Concomitant Immunogenicity Evaluation

All the primary concomitant immunogenicity endpoints/estimands are considered coprimary in the study. For the primary concomitant immunogenicity objective comparing immune responses induced by concomitant vaccine antigens from the 20vPnC group to that from the 13vPnC group, NI is assessed by hypothesis tests as stated in Section 9.1.2.2, at a significance level of 0.05 for each of the concomitant vaccine antigens, including diphtheria toxoid, tetanus toxoid, PT, FHA, PRN, HBsAg, poliovirus strains, Hib, measles, mumps, rubella, and varicella. The primary concomitant immunogenicity objective will be met if NI is achieved for each concomitant vaccine antigen. Therefore, the type I error rate for the concomitant immunogenicity assessment is well controlled at the 0.05 level.

9.2. Sample Size Determination

The sample size of the study is determined primarily based on considerations of 1) accumulating a sufficient overall safety database for the 20vPnC infant clinical development program, 2) providing robust assessment of the pneumococcal immune responses induced by 20vPnC and 13vPnC, 3) ensuring robust assessment to demonstrate that the immune responses induced by concomitant vaccine antigens given with 20vPnC are noninferior to immune responses induced by concomitant vaccine antigens given with 13vPnC, and 4) practical constraints of available serum volumes from individual study participants with all planned immunogenicity assessments.

9.2.1. Sample Size Consideration for the Primary Pneumococcal Immunogenicity Objectives for the Primary Study Population

The study power for the primary pneumococcal immunogenicity objectives is assessed based on simulations of multivariate log-normal distributed random numbers with assumptions supported by IgG results after 2 and/or 3 infant doses from historical 13vPnC and 7vPnC infant studies, and IgG results after 3 infant doses and the toddler dose of an internal Phase 2 infant study of 20vPnC (B7471003).

For the immune response 1 month after 2 infant doses of 20vPnC, serotype-specific IgG GMCs and the variance-covariance matrix are assumed to be the same as those estimated from Study B7471003 1 month after 3 infant doses of 20vPnC, after adjustments made based on the observed relationship between IgG results after 2 infant doses and after 3 infant doses in the historical studies. To accommodate the uncertainties in the assumptions, 3 different assumed GMRs of the 20vPnC to the 13vPnC group 1 month after Dose 2 are explored to evaluate the study power in the simulation [redacted]

For the immune response 1 month after Dose 3 (toddler dose), the true GMCs and variance-covariance matrices for the 20 serotype-specific IgG concentrations from both the 20vPnC and 13vPnC groups are assumed to be the same as the IgG results 1 month after Dose 4 from Study B7471003 (3 infant doses and a toddler dose).

With approximately 1200 enrolled participants using a 1:1 randomization ratio, assuming a 10% nonevaluable rate at 1 month after Dose 2, and a 17% nonevaluable rate at 1 month after

Dose 3, the study will result in approximately 540 and 500 evaluable participants for each vaccine group at 1 month after Dose 2 and 1 month after Dose 3, respectively. Under the 3 IgG GMR assumptions, the study has approximately 99%, 97%, and 85% probability, respectively, to show NI of 20vPnC to 13vPnC for at least 47 (out of 60 total) positive NI assessments comparing IgG results CCI CCI

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9.2.2. Sample Size Consideration for the Primary Concomitant Immunogenicity Objective

For the primary concomitant immunogenicity objective, the size of the subset of study participants for each assay will be determined based on the serum volume required and available samples for testing, in addition to the statistical power for each concomitant antigen.

Table 5 provides the minimum evaluable sample size required to demonstrate NI with the specified power for percentage of participants with prespecified antibody level to each concomitant vaccine antigen at 1 month after Dose 3. A 10% NI margin is used for each concomitant vaccine antigen. The estimates of response rates for the concomitant antigens were taken from a Pfizer infant study of 13vPnC. With a target power of 99% for each concomitant antigen, the number of evaluable participants in each vaccine group needed ranges from 36 to 502. If the target power for each concomitant antigen is 95%, the evaluable sample size per group reduces to a range of 36 to 362 per group.

Table 5. Sample Size Required With Specified Power to Demonstrate NI Comparing the 20vPnC Group to the 13vPnC Group Based on Percentage of Participants Who Reached Prespecified Antibody Levels for Concomitant Antigens, With 10% NI Margin

Antigen	Antibody Level Threshold	Assumed Percentage[a] of Participants Achieving Prespecified Threshold		Evaluable Sample Size per Vaccine Group With at Least	
		20vPnC	13vPnC	95% Power	99% Power
Diphtheria	≥0.1 IU/mL	100	100	36	36
Tetanus	≥0.1 IU/mL	97	97	116	154
PT	≥ Concentration achieved by 95% of 13vPnC group	92	95	362	502
FHA	≥ Concentration achieved by 95% of 13vPnC group	95	95	155	212
PRN	≥ Concentration achieved by 95% of 13vPnC group	94	95	201	276
Hepatitis B	≥10 mIU/mL	97	98	127	167
Polio 1	≥1:8	100	100	36	36
Polio 2	≥1:8	100	100	36	36
Polio 3	≥1:8	100	100	36	36

Table 5. Sample Size Required With Specified Power to Demonstrate NI Comparing the 20vPnC Group to the 13vPnC Group Based on Percentage of Participants Who Reached Prespecified Antibody Levels for Concomitant Antigens, With 10% NI Margin

Antigen	Antibody Level Threshold	Assumed Percentage[a] of Participants Achieving Prespecified Threshold		Evaluable Sample Size per Vaccine Group With at Least	
		20vPnC	13vPnC	95% Power	99% Power
Haemophilus influenzae type B	≥0.15 µg/mL	99	99	72	90

Abbreviations: FHA = filamentous hemagglutinin; NI = noninferiority; PRN = pertactin; PT = pertussis toxin.
Note: NI criterion for each concomitant antigen: the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages of participants who reached the prespecified threshold is above -10%, calculated using the Miettinen and Nurminen method.

a. The differences between 20vPnC and 13vPnC are assumed to be similar to those observed between 13vPnC and 7vPnC from Phase 3 Prevnar 13 Study 6096A1-500. Percentages of participants who reached specified thresholds from 13vPnC are assumed to be the same as those observed in 13vPnC groups from Phase 3 Prevnar 13 Study 6096A1-500 with a similar design.

Table 6 presents the minimum evaluable sample size required to demonstrate NI with specified power for GMC comparisons of the 20vPnC group to the 13vPnC group for antibody levels to measles, mumps, rubella, and varicella antigens 1 month after Dose 3. A 2-fold NI margin is used for each concomitant vaccine antigen. The GMRs of antibody levels to each concomitant vaccine antigen from the 20vPnC group to that from the 13vPnC group and their standard deviations are assumed to be similar to those observed from a Pfizer Phase 3 13vPnC study in the power calculations (Table 6). With a target power of 99% for each of the measles, mumps, rubella, and varicella antigens, the evaluable sample size for each group ranges from 20 to 240. The evaluable sample size per group lowers to 15 to 171 for a target power of 95% per antigen.

Table 6. Sample Size Required With Specified Power to Demonstrate NI of 20vPnC to 13vPnC Based on GMCs of Antibody Levels to Concomitant Vaccine Antigens, With a 2-Fold NI Margin

Antigen	Assumed GMR[a] for 20vPnC vs 13vPnC	Assumed Standard Deviation GMR[a] (on the Natural Log Scale)	Evaluable Sample Size per Vaccine Group With at Least	
			95% Power	99% Power
Measles	0.98	0.654	26	36
Mumps	1.00	0.743	31	44
Rubella	0.83	1.294	171	240
Varicella Ig	1.00	0.497	15	20

Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; Ig = immunoglobulin; NI = noninferiority.

Note: NI criterion for each serotype: lower bound of the 2-sided 95% CI for GMR (20vPnC over 13vPnC) is greater than 0.5, calculated using a t-distribution.

a. The GMR of the 20vPnC group to the 13vPnC group and the standard deviations are assumed to be similar to those observed from the 13vPnC and 7vPnC groups in Study 6096A1-004.

9.2.3. Sample Size Consideration for the Primary Safety Objective

The primary safety objective includes the endpoints for AEs, local reactions, and systemic events. The number of participants in each vaccine group is 600, which provides a greater than 90% chance of observing at least 1 AE, local reaction, or systemic event in a group, assuming a true rate of at least 0.4% (Table 7).

Table 7. Probability of Detecting at Least 1 Adverse Event

Sample Size per Group	True Rate of AEs	Probability of Observing at Least 1 AE
600	0.1%	45.1%
	0.2%	69.9%
	0.3%	83.5%
	0.4%	91.0%
	0.5%	95.1%

9.2.4. Sample Size Consideration for the Russian Cohort

The sample size for the Russian cohort is not driven by statistical power. There is no hypothesis test for the data in the Russian cohort. The safety and pneumococcal immunogenicity data from the Russian cohort will be descriptively summarized.

9.3. Populations for Analysis

For purposes of analysis, the following participant populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Dose 2 evaluable immunogenicity	All eligible randomized participants who are within the protocol-defined age window on the day of first vaccination, receive the vaccines to which they are randomly assigned at the first 2 doses, have at least 1 valid immunogenicity result from the 1-month-after-Dose 2 visit, have blood collection within an appropriate window for this visit, and have no other major protocol deviations as determined by the clinician.
Dose 3 evaluable immunogenicity	All eligible randomized participants who are within the protocol-defined age window on the day of first vaccination, receive all 3 randomized vaccinations, with Dose 3 received within the protocol-defined age window, have at least 1 valid immunogenicity result from the 1-month-after-Dose 3 visit, have blood collection within an appropriate window at this visit, and have no other major protocol deviations as determined by the clinician.
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Safety	All participants who receive at least 1 dose of the investigational product and have safety data assessed after any dose.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for the final analysis and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, CCI endpoints.

9.4.1. Immunogenicity Analysis

The statistical analysis of the pneumococcal immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3. The statistical analysis of concomitant immunogenicity results will be primarily based on the evaluable immunogenicity populations among those who receive the appropriate concomitant vaccines.

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Participants will be summarized according to the vaccine group to which they were randomized.

Endpoint	Statistical Analysis Methods
Primary pneumococcal immunogenicity	• **Percentages of participants with predefined pneumococcal IgG concentrations 1 month after Dose 2** For each of the 20 serotypes, the difference between groups (20vPnC – 13vPnC) and its 2-sided 95% CI for the percentage of participants with predefined IgG concentrations 1 month after Dose 2 will be provided. If a serotype is from the 13 matched serotypes, the percentage of participants with the predefined IgG level for the serotype in the 20vPnC group will be compared with the percentage for that serotype in the 13vPnC group. If a serotype is from the 7 additional serotypes, the percentage of participants with the predefined IgG level in the 20vPnC group will be compared with the lowest percentage among the 13 serotypes from the 13vPnC group, provided that the lowest percentage is not from serotype 3. If the lowest percentage in the 13vPnC group is from serotype 3, the next lowest percentage in the 13vPnC group will be used in the comparison. The Miettinen and Nurminen method will be used to derive the CI for the difference in percentages between vaccine groups. The lower limit of the CI will be used in the hypothesis test for NI of 20vPnC to 13vPnC as detailed in Section 9.1.2.1.1. In addition, for each of the 7 additional serotypes, the difference between groups (20vPnC – 13vPnC) with the comparator being the percentage of participants achieving predefined IgG concentrations for that corresponding serotype from the 13vPnC group will be calculated. The 2-sided 95% CI for the difference will also be based on the Miettinen and Nurminen method. The analysis will be based on the Dose 2 evaluable immunogenicity population. CCI CCI

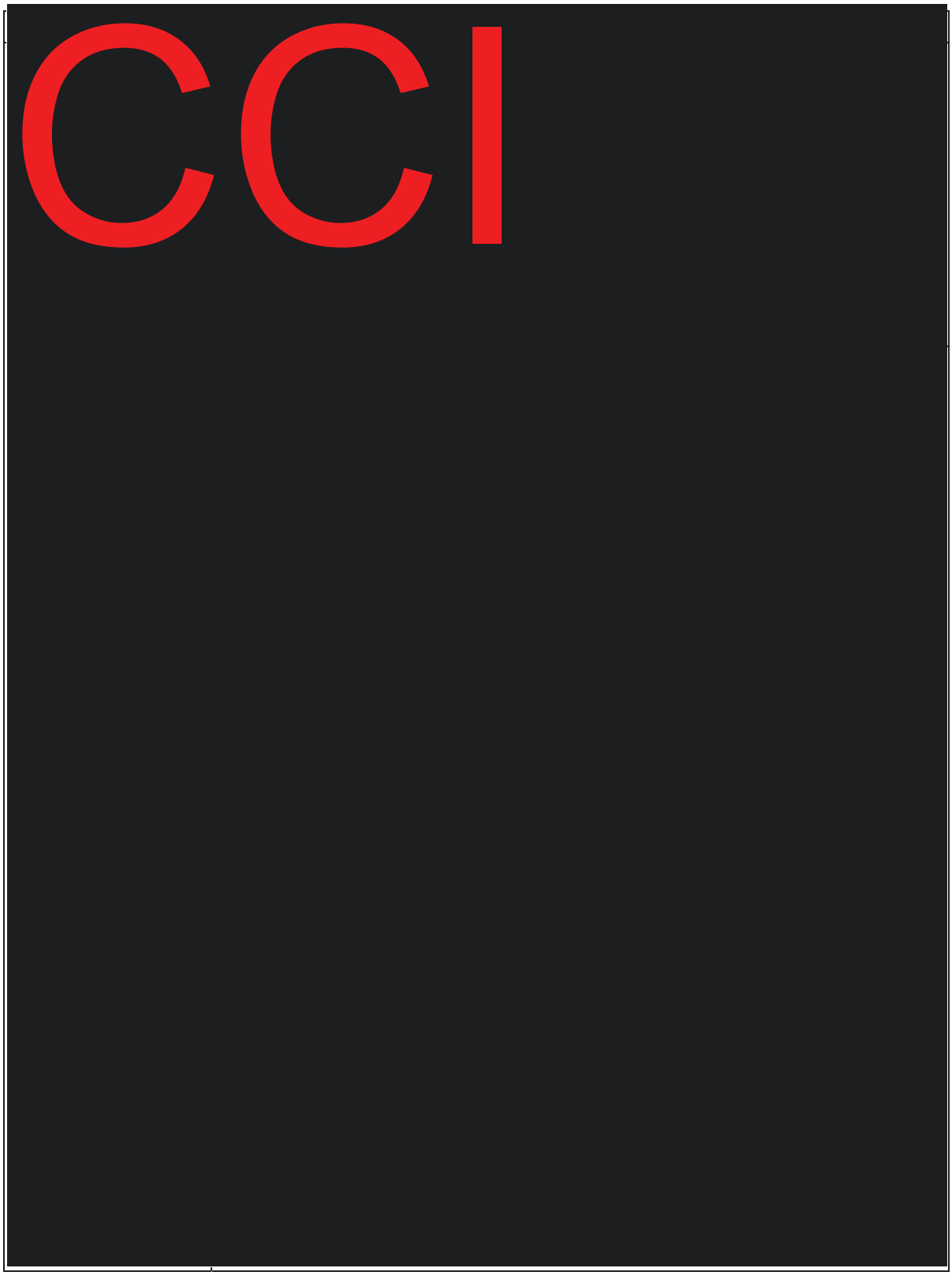
Endpoint	Statistical Analysis Methods
	CCI CCI Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. • **GMRs of pneumococcal IgG concentrations from the 20vPnC group to the 13vPnC group 1 month after Dose 2** For each of the 20 serotypes, the GMR of 20vPnC to 13vPnC at 1 month after Dose 2 will be provided. If a serotype is from the 13 matched serotypes, the IgG GMC for the serotype in the 20vPnC group will be compared with the IgG GMC for that serotype in the 13vPnC group. If the serotype is from the 7 additional serotypes, the IgG GMC in the 20vPnC group will be compared with the lowest IgG GMC among the 13 serotypes from the 13vPnC group, provided that the lowest GMC is not from serotype 3. If the lowest GMC in the 13vPnC group is from serotype 3, the next lowest GMC in the 13vPnC group will be used in the comparison. GMRs and their 2-sided 95% CIs will be derived by calculating differences in means and CIs on the natural log scale of the concentration based on the t-distribution, and then exponentiating the results. The difference in means, on the natural log scale, will be 20vPnC minus 13vPnC. The lower limit of the CI will be used in the hypothesis test for NI of 20vPnC to 13vPnC as detailed in Section 9.1.2.1.2. In addition, for each of the 7 additional serotypes, the GMR of 20vPnC to 13vPnC at 1 month after Dose 2 with the comparator being the IgG GMC of that serotype in the 13vPnC group will be calculated. GMRs and their 2-sided 95% CIs will be derived in the same way as described above. The analyses will be based on the Dose 2 evaluable immunogenicity population. CCI CCI CCI Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

Endpoint	Statistical Analysis Methods
	• **GMRs of pneumococcal IgG concentrations from the 20vPnC group to the 13vPnC group 1 month after Dose 3** The IgG GMRs at 1 month after Dose 3 will be analyzed the same way as the IgG GMRs at 1 month after Dose 2. The lower limit of the CI of the GMR will be used in the hypothesis test for NI of 20vPnC to 13vPnC as detailed in Section 9.1.2.1.3.
Primary concomitant immunogenicity	• **Percentages of participants with prespecified antibody levels to specific concomitant vaccine antigens (diphtheria, tetanus, pertussis, HBsAg, polio, and Hib) at 1 month after Dose 3** For each of the concomitant vaccine antigens, a. Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN), b. Antibody levels to HBsAg, c. Antibody levels to poliovirus strains (types 1, 2, and 3), and d. Antibody levels to Hib. The difference between the groups (20vPnC – 13vPnC) and its 2-sided 95% CI for the percentage of participants with prespecified antibody levels 1 month after Dose 3 will be provided. The Miettinen and Nurminen method will be used to derive the CI for the difference in percentages between vaccine groups. The lower limit of the CI will be used in the hypothesis test for NI of 20vPnC group to 13vPnC group as detailed in Section 9.1.2.2.1. • **GMRs in antibody levels to measles, mumps, rubella, and varicella viruses at 1 month after Dose 3** For each antibody level to measles, mumps, rubella, and varicella viruses, the GMR of the 20vPnC group to the 13vPnC group at 1 month after Dose 3 will be provided. GMRs and their 2-sided 95% CIs will be derived by calculating differences in means and CIs on the natural log scale of the concentrations based on the t-distribution, and then exponentiating the results. The difference in means, on the natural log scale, will be 20vPnC minus 13vPnC. The lower limit of the CI will be used in the hypothesis test for NI of 20vPnC to 13vPnC as detailed in Section 9.1.2.2.2. The analysis will be based on the Dose 3 evaluable immunogenicity population, restricted to those who also receive the corresponding concomitant vaccines. An additional analysis will be performed based on the Dose 3 all-available immunogenicity population among those who also receive the corresponding concomitant vaccine, if there is a large enough difference in sample size between the all-available immunogenicity

Endpoint	Statistical Analysis Methods
	population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary pneumococcal immunogenicity	• **Percentages of participants with predefined pneumococcal IgG concentrations 1 month after Dose 3** This endpoint will be analyzed in the same way as the percentages of participants with predefined pneumococcal IgG concentrations 1 month after Dose 3, except that no hypothesis test for NI will be performed. • **GMTs of OPA 1 month after Dose 2 and 1 month after Dose 3** For each of the 20 serotypes in 20vPnC, the GMTs and 2-sided 95% CIs for the OPA titers at each time point will be provided for each vaccine group. Geometric means and the associated 2-sided 95% CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, and then exponentiating the results. • **GMFRs of pneumococcal IgG concentrations from before Dose 3 to 1 month after Dose 3 in each vaccine group** For each of the 20 serotypes in 20vPnC, the GMFR and 2-sided 95% CI for IgG concentrations from before Dose 3 to 1 month after Dose 3 will be provided for each vaccine group. GMFRs will be limited to participants with nonmissing values at both time points. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (1 month after Dose 3 – before Dose 3) and transformed back to the original scale. Two (2)-sided 95% CIs will be obtained by calculating the CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the limits back to the original scale.
Secondary concomitant immunogenicity	• **Percentages of participants with prespecified antibody levels to specific concomitant vaccine antigens (diphtheria, tetanus, pertussis, polio, and Hib) 1 month after Dose 2** Percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), poliovirus strains, and Hib 1 month after Dose 2 will be provided for each vaccine group, along with 2-sided Clopper-Pearson 95% CIs. The differences between the groups

Endpoint	Statistical Analysis Methods
	(20vPnC – 13vPnC) in these percentages and the associated 2-sided Miettinen and Nurminen 95% CIs will be calculated.

CCI


CCI

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary safety	• Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs. Between-group differences (20vPnC – 13vPnC) in these percentages and their 2-sided 95% CIs will also be provided. The Miettinen and Nurminen method will be used to derive the 95% CI for the difference in percentages between vaccine groups. • AEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3-tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, the 2-sided 95% CIs for the difference in percentage of participants reporting the events between the 20vPnC and 13vPnC groups will be calculated using the Miettinen and

Endpoint	Statistical Analysis Methods
	Nurminen method. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. There is no Tier 1 event identified for 20vPnC at this stage. Descriptive summary statistics (counts, percentages, and associated 2-sided Clopper-Pearson 95% CIs) will be provided for Tier 3 events for each vaccine group. • SAEs and NDCMCs will be categorized according to MedDRA terms. Counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs for SAEs and NDCMCs will be provided for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	• Not applicable (N/A)
CCI	

9.4.3. Other Analyses

The safety and pneumococcal immunogenicity data from the Russian cohort will be descriptively summarized separately.

9.5. Interim Analyses

No interim analysis is planned in this study.

9.5.1. Analysis Timing

The safety and immunogenicity results in this study will be analyzed and reported when the safety and immunogenicity data 1 month after Dose 3 are available from all participants in the primary study population.

The safety and pneumococcal immunogenicity results of the Russian cohort will be analyzed and reported when safety and pneumococcal immunogenicity data are available from all participants in the Russian cohort.

Sponsor personnel involved in evaluating participant data in the primary study population will be blinded to vaccine assignment until the analysis at the completion of the primary study population. The study team will remain blinded to the vaccine assignments of the Russian cohort until that cohort has completed the study. Laboratory personnel performing

the assays will remain blinded until all assays are completed and assay results of each population/cohort are finalized.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, IB, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant's parent(s)/legal guardian(s) and answer all questions regarding the study.

The participant's parent(s)/legal guardian(s) must be informed that participation is voluntary. The participant's parent(s)/legal guardian(s) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian(s) is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant's parent(s)/legal guardian(s) must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/legal guardian(s).

The participant's parent(s)/legal guardian(s) must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant's parent(s)/legal guardian(s) is fully informed about his or her right to access and correct the participant's personal data and to withdraw consent for the processing of the participant's personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

The participant's parent(s)/legal guardian(s) must be reconsented to the most current version of the ICD(s) during the participant's participation in the study.

A copy of the ICD(s) must be provided to the participant's parent(s)/legal guardian(s).

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

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

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development;
- Study completion of the applicable population or cohort.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 18 months after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, the participant's parent(s)/legal guardian(s) are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study.

The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not

available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant's parent(s)/legal guardian(s) directly, and if a participant's parent(s)/legal guardian(s) calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Events that, in the clinical judgment of the investigator, are 1) consistent with normal growth and development and 2) do not differ significantly in frequency or severity from expected, are not generally to be considered AEs. Examples may include, but are not limited to, teething, contact diaper rash, spitting up, colic, or typical fussiness/crying in infants and children. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of NDCMC

An NDCMC is defined as a significant disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects.

10.3.3. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

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

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

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

Assessment of Causality

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

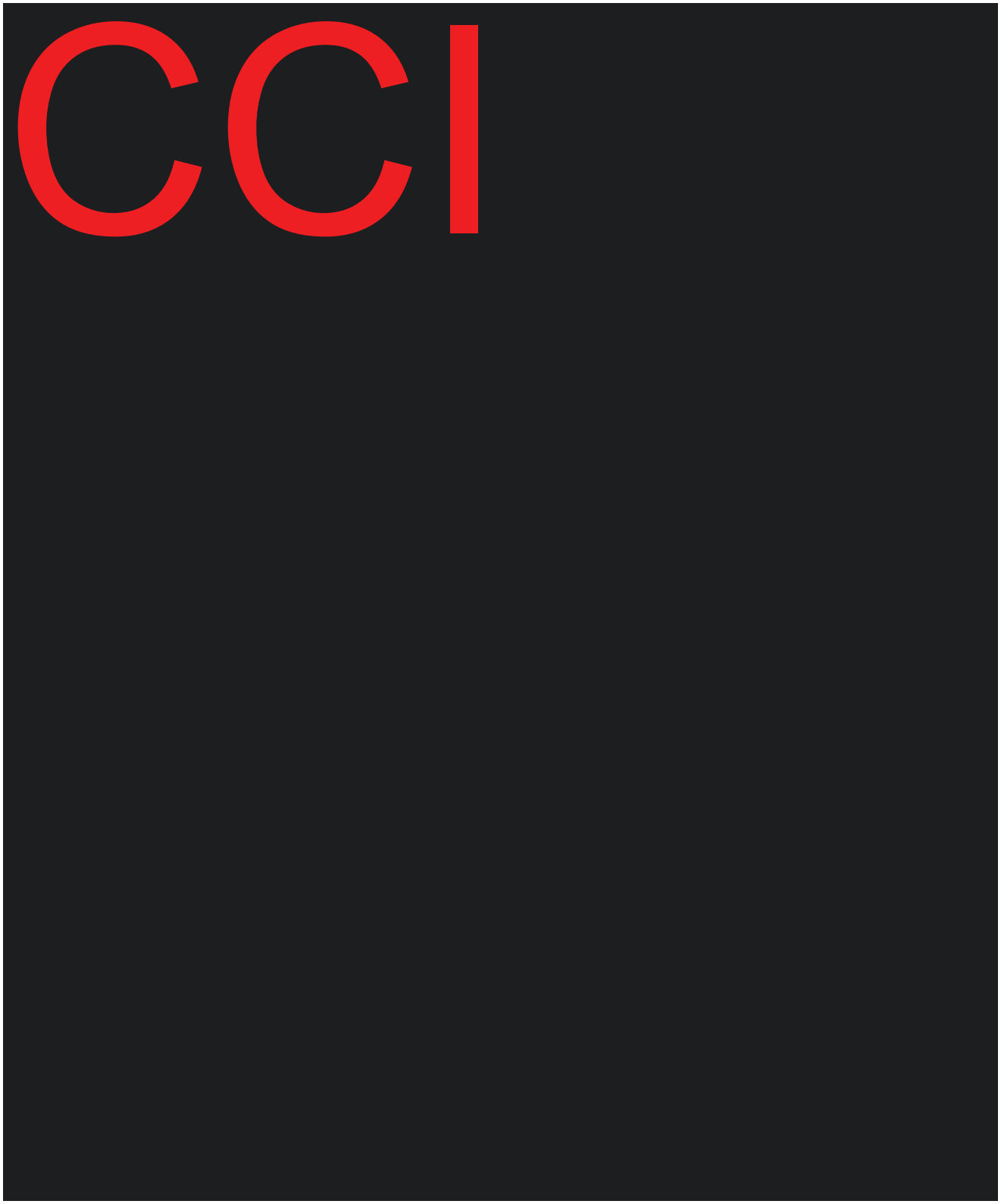
Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.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10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

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

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

Not applicable.

10.8. Appendix 8: Medical Device Adverse Events, Adverse Device Effects (ADEs), Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, Serious Adverse Device Effect (SADE), and Unanticipated Serious Adverse Device Effect (USADE)

- If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.8.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP manual.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/Device Deficiency
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.8.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.9. Appendix 9: Country-Specific Appendix – Applicable to Italy Only

The following supplementary text should be read in conjunction with the applicable sections of the protocol.

10.9.1. Exclusion Criterion 1 Clarification

Exclusion criterion 1 (Section 5.2) reads, "History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of investigational product or any diphtheria toxoid–containing vaccine". As specified in Section 6, the concomitant study vaccines (DTaP, HBV, IPV, and Hib vaccine, MMR vaccine, and varicella vaccine), which are provided by Pfizer, are considered to be investigational product when administered as part of the study and are described as such in the IP manual. The authorized product SmPCs should be referenced for contraindications for the DTaP, HBV, IPV and Hib vaccine, MMR vaccine, and varicella vaccine (the vaccine-specific SRSDs referred to in Section 2.3). The SmPC for each of the vaccines is provided in the ISF.

10.9.2. Clarification of Route of Administration of Concomitant Study Vaccines

Section 6.1 describes the study interventions, including the concomitant study vaccines, and refers to the IP manual and SRSDs (ie, SmPC) for each of the vaccines. Section 6.1.1 describes the route of administration of concomitant study vaccines, and the wording allows for flexibility of supply or sourcing of vaccines that might have different routes of administration. The IP manual is referred to in the protocol and is provided to all investigator sites. It is also referred to during investigator site training as the document to guide preparation and administration of study vaccines. The IP manual, along with the SRSDs, should be referenced for the specific routes of administration for the concomitant vaccines being used in the study, which are as follows:

- DTaP, HBV, IPV, and Hib vaccine is to be administered intramuscularly.
- MMR vaccine is to be administered intramuscularly or subcutaneously.
- Varicella vaccine is to be administered subcutaneously.

10.10. Appendix 10: Russian Cohort

10.10.1. Summary of Protocol Modification Specific to the Russian Cohort

The following list summarizes the modifications of the protocol that are specific to the Russian cohort.

- The Russian cohort will consist of approximately 60 participants randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC. Enrollment of the Russian cohort is projected to commence after enrollment of the primary study population is complete.
- The inclusion criterion for age is ≥42 to ≤70 days of age (within the range, but a slightly more narrow window than the primary study population).
- The parents/legal guardians of Russian cohort participants CCI [redacted] CCI but the blood draws at Visits 3, 4, and 5 are required (see the SoA in Section 10.10.2).
- Participants in the Russian cohort will not receive MMR and varicella vaccinations as part of the study. Instead, they will receive MMR and varicella as per local requirements/NIP.
- The timing of visits for participants has been slightly modified for the Russian cohort, to align with the Russian NIP (see the SoA for the Russian cohort below, Section 10.10.2) and the age range for Dose 3 vaccination is wider (with an older upper age limit of 15 months). This also results in the potentially longer duration of study participation than the primary study population noted in Section 4.1.1 of the protocol.
- Concomitant vaccine antigen responses will not be assessed.
- The Russian cohort data will be summarized separately and descriptively. No formal hypothesis test is planned.

10.10.2. Schedule of Activities for Russian Cohort

Visit Number	1	2	3	4	5
Visit Description	**Dose 1 Visit**	**Dose 2 Visit**	**Dose 2 Follow-up Visit**	**Dose 3 Visit**	**Dose 3 Follow-up Visit**
Visit Window (Days)	**≥42 to ≤70 Days After Birth**	**60 to 90 Days After Visit 1**	**28 to 42 Days After Visit 2**	**335 to 455 Days of Age**	**28 to 42 Days After Visit 4**
Obtain informed consent	X				
Assign participant number via the IRT	X				
Review inclusion and exclusion criteria	X				
Record demography	X				
Perform clinical assessment, including medical history	X				
Record vaccine history	X				
Provide parent(s)/legal guardian(s) with a contact card	X				
Obtain prevaccination temperature (measured as appropriate for age)	X	X		X	
Record nonstudy vaccinations and concomitant medications[a]	X	X	X	X	X
Record vaccines administered during pregnancy and intrapartum antibiotic use (yes/no) (if available)	X[b]				
Review temporary delay criteria	X	X	X	X	X
Review continued eligibility		X	X	X	X
Assign randomization number	X				
Obtain ~5-mL blood sample			X	X[c]	X
Administer investigational product in the left thigh[d]	X	X		X	
Administer specific concomitant vaccine	X[e]	X[e]		X[e]	
Observe and record any reactions for 30 minutes after investigational vaccine administration	X	X		X	
Provide parent(s)/legal guardian(s) with an e-diary (device or application, as appropriate), digital thermometer, and measuring device and instruct to collect prompted local reactions and systemic events 7 days after vaccination[f]	X	X		X	
Review e-diary[g]		X	X		X
Collect e-diary (if applicable)			X		X

Visit Number	1	2	3	4	5
Visit Description	**Dose 1 Visit**	**Dose 2 Visit**	**Dose 2 Follow-up Visit**	**Dose 3 Visit**	**Dose 3 Follow-up Visit**
Visit Window (Days)	**≥42 to ≤70 Days After Birth**	**60 to 90 Days After Visit 1**	**28 to 42 Days After Visit 2**	**335 to 455 Days of Age**	**28 to 42 Days After Visit 4**
Record and report AEs[h]	X----------X			X ----------X	
Record and report SAEs and NDCMCs[h,i]	X----------X				

Abbreviations: DTaP = diphtheria, tetanus, and acellular pertussis vaccine; e-diary = electronic diary; HBV = hepatitis B virus; Hib = *Haemophilus influenzae* type b; ICD = informed consent document; IPV = inactivated poliovirus vaccine; IRT = interactive response technology; NDCMC = newly diagnosed chronic medical condition.

a. Record concomitant medications used to treat SAEs and NDCMCs from the signing of the ICD to the final visit (Visit 5).
b. Vaccines administered during pregnancy and intrapartum antibiotic use (yes or no) will be collected at Visit 1 only (if available).
c. Blood sample will be collected prior to vaccination.
d. Remind the participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.
e. The participant will receive a specific vaccine containing DTaP, HBV, IPV, and Hib antigens at 2, 4.5, and 11 to 15 months of age (Visit 1, Visit 2, and Visit 4, respectively). This vaccine(s) will be given in a limb other than the site of administration of 20vPnC or 13vPnC.
f. The participant's parent(s)/legal guardian(s) will record prompted local reactions and systemic events in an e-diary for the 7 days following each dose of 20vPnC or 13vPnC. Use of antipyretic/pain medications will also be prompted for and collected daily in the e-diary for 7 days after vaccination. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling >14 caliper units, severe pain at the 20vPnC or 13vPnC injection site, a fever >40.0°C (>104.0°F), an emergency room visit, or hospitalization.
g. Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 7 days following each dose of 20vPnC or 13vPnC to evaluate participant compliance and reported events as part of the ongoing safety review.
h. If the parent(s)/legal guardian(s) consents, participants withdrawn from the study will have any new AEs, SAEs, and NDCMCs collected for 1 month after their last study vaccination.
i. An NDCMC is a significant disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects.

10.10.3. Objectives, Estimands, and Endpoints for Russian Cohort

Safety Objective	Estimands	Safety Endpoints
To describe the safety profile of 20vPnC	In participants (primary study population and Russian cohort combined) receiving at least 1 dose of investigational product and having safety data reported after any vaccination in each vaccine group: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination • The percentage of participants reporting prompted systemic events within 7 days after each vaccination • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3 • The percentage of participants reporting SAEs through 1 month after Dose 3 • The percentage of participants reporting NDCMCs through 1 month after Dose 3	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs
Primary Pneumococcal Immunogenicity Objective	**Estimands**	**Primary Pneumococcal Immunogenicity Endpoints**
To describe the IgG responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC for each vaccine group: • Percentages of participants with predefined IgG concentrations at 1 month after Dose 2 • IgG GMCs at 1 month after Dose 2 • IgG GMCs at 1 month after Dose 3	• Pneumococcal IgG concentrations • Pneumococcal OPA titers
Secondary Pneumococcal Immunogenicity Objective	**Estimands**	**Secondary Pneumococcal Immunogenicity Endpoints**
To further describe immune responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC for each vaccine group: • Percentages of participants with predefined IgG concentrations at 1 month after Dose 3 • OPA GMTs at 1 month after Dose 2 • OPAs GMTs at 1 month after Dose 3	• Pneumococcal IgG concentrations • Pneumococcal OPA titers

10.10.4. Notes on the Russian National Immunization Program

The following table includes information about the National Immunization Schedule of the Russian Federation for children 0 through 18 months of age:

NATIONAL IMMUNIZATION SCHEDULE (Partial)[75] List of amending documents (as amended by Orders of the Ministry of Health of Russia No. 370н dated 16 June 2016, No. 175н dated 13 April 2017, No. 243н dated 24 April 2019, No. 967н dated 14 September 2020)	
Categories and age of citizens subject to compulsory vaccination	**Immunization name**
Newborns in the first 24 hours of life	First vaccination against hepatitis B virus[a]
Newborns, on the 3rd - 7th day of age	Vaccination against tuberculosis[b]
Children of 1 month of age	Second vaccination against hepatitis B virus[a]
Children of 2 months of age	Third vaccination against hepatitis B virus (risk groups)[c]
	First vaccination against pneumococcal infection
Children of 3 months of age[d]	First vaccination against diphtheria, pertussis, tetanus
	First vaccination against poliomyelitis[e]
	First vaccination against *Haemophilus influenzae* (risk groups)[f]
(as amended by Order of the Ministry of Health of Russia of No. 175н dated 13 April 2017)	
Children of 4.5 months of age[d]	Second vaccination against diphtheria, pertussis, tetanus
	Second vaccination against *Haemophilus influenzae* (risk groups)[f]
	Second vaccination against poliomyelitis[e]
	Second vaccination against pneumococcal infection
(as amended by Order of the Ministry of Health of Russia of No. 175н dated 13 April 2017)	

NATIONAL IMMUNIZATION SCHEDULE (Partial)[75] List of amending documents (as amended by Orders of the Ministry of Health of Russia No. 370н dated 16 June 2016, No. 175н dated 13 April 2017, No. 243н dated 24 April 2019, No. 967н dated 14 September 2020)	
Categories and age of citizens subject to compulsory vaccination	**Immunization name**
Children of 6 months of age[d]	Third vaccination against diphtheria, pertussis, tetanus
	Third vaccination against hepatitis B virus[a]
	Third vaccination against poliomyelitis[g]
	Third vaccination against *Haemophilus influenzae* (risk group)[f]
(as amended by Order of the Ministry of Health of Russia of No. 175н dated 13 April 2017)	
Children of 12 months of age	Vaccination against measles, rubella, mumps
	Fourth vaccination against hepatitis B virus (risk groups)[c]
Children of 15 months of age	Revaccination against pneumococcal infection
Children of 18 months of age[d]	First revaccination against poliomyelitis[g]
	First revaccination against diphtheria, pertussis, tetanus
	Revaccination against *Haemophilus influenzae* (risk groups)
(as amended by Order of the Ministry of Health of Russia of No. 175н dated 13 April 2017)	

a. First, second, and third vaccinations are carried out according to the 0-1-6 schedule (1st dose - at the start of vaccination, 2nd dose - one month after the 1st vaccination, 3rd dose - 6 months after the start of vaccination), with the exception of children belonging to risk groups, for whom the vaccination against hepatitis B virus is carried out according to the 0-1-2-12 schedule (1st dose - upon start of the vaccination, 2nd dose - one month after the 1st vaccination, 3rd dose - 2 months after the start of vaccination, 4th dose - 12 months after the start of vaccination).

b. Vaccination is carried out with a tuberculosis vaccine for attenuated primary vaccination (BCG-M, ie, modified BCG vaccine); in the constituent entities of the Russian Federation with morbidity rates exceeding 80 per 100,000 population, as well as in the presence of tuberculosis patients in the environment of a newborn - a tuberculosis vaccine (BCG vaccine).

c. Vaccination is carried out for children belonging to risk groups (born from mothers carrying HBsAg, HBV or who have had HBV in the third trimester of pregnancy, who do not have blood test results for hepatitis B markers, who use narcotic drugs or psychotropic substances, from families with a carrier of HBsAg or a patient with acute HBV and chronic viral hepatitis).

d. Vaccination and revaccination of children at risk can be carried out with immunobiological drugs for immunoprophylaxis of infectious diseases, containing combinations of vaccines to be used at appropriate age periods.
(footnote introduced by Order of the Ministry of Health of Russia No. 175н dated 13 April 2017)

e. First and second vaccinations are carried out with the polio vaccine (inactivated).

f. Vaccination is carried out for children belonging to risk groups (with diseases of the nervous system, immunodeficiency disorders, or anatomical defects leading to a sharply increased risk of hemophilic infection; with intestinal malformations; with oncological diseases and/or receiving immunosuppressive therapy for a long time; children born to mothers with HIV infection; children with HIV infection; premature and low-birth-weight children; children in orphanages).
(footnote as amended by Order of the Ministry of Health of Russia of No. 243н dated 24 April 2019)

g. Third vaccination and subsequent revaccinations of children against poliomyelitis are carried out with the polio vaccine (live); children belonging to risk groups (with diseases of the nervous system, immunodeficiency disorders, or anatomical defects leading to a sharply increased risk of hemophilic infection; with intestinal malformations; with oncological diseases and/or receiving long-term immunosuppressive therapy; children born to mothers with HIV infection; children with HIV infection; premature and low-birth-weight children; children in orphanages) - with the polio vaccine (inactivated).
(footnote as amended by Order of the Ministry of Health of Russia of No. 243н dated 24 April 2019)

The use of Infanrix hexa will provide the concomitant vaccine antigens of diphtheria, tetanus, acellular pertussis, hepatitis B, poliovirus, and *Haemophilus influenzae* type b (DTaP, HBV, IPV, and Hib) and be administered at approximately 2, 4.5, and 11 to 15 months of age with the blinded study vaccine (20vPnC or 13vPnC [control vaccine]). Although the administration of Infanrix hexa will be given on a slightly different schedule than the National Immunization Schedule of the Russian Federation noted above, numerous studies of Infanrix hexa have demonstrated that an immunization schedule of 2 infant doses and a toddler dose will provide protection against the diseases covered by the vaccine. Based on data in the Russian Infanrix hexa SmPC, the 2-dose and 3-dose primary vaccination schedules have similar overall seroprotective or seropositive antibody levels against each of the vaccine antigens.

Therefore, Infanrix hexa use in this study in accordance with a 2-dose primary and booster schedule is consistent with the manufacturer's label for providing appropriate and adequate protection of the infant against the aforementioned diseases.

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
20vPnC	20-valent pneumococcal conjugate vaccine
AE	adverse event
ADE	adverse device effect
ADL	activity(ies) of daily living
ALT	alanine aminotransferase
AOM	acute otitis media
AST	aspartate aminotransferase
BCG	bacille Calmette-Guérin
CAP	community-acquired pneumonia
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CLIA	chemiluminescent immunoassay
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRM_{197}	cross-reactive material 197
CRO	contract research organization
CSAP	clinical specimen assessment plan
CSR	clinical study report
DILI	drug-induced liver injury
DTaP	diphtheria, tetanus, and acellular pertussis vaccine
DU	dispensable unit
EC	ethics committee
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
CCI	[redacted]
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
ELISA	enzyme-linked immunosorbent assay

Abbreviation	Term
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FHA	filamentous hemagglutinin
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
Hib	*Haemophilus influenzae* type b
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IPD	invasive pneumococcal disease
IPV	inactivated poliovirus vaccine
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
IU	international unit(s)
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles, mumps, and rubella vaccine
N/A	not applicable
NA	neutralizing antibody
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
NIP	national immunization program
OPA	opsonophagocytic activity

Abbreviation	Term
PCD	primary completion date
PPSV23	23-valent pneumococcal polysaccharide vaccine
PRN	pertactin
PRP	polyribosylribitol phosphate
PT	pertussis toxin
CCI	[redacted]
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	summary of product characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
VT	vaccine-type
WHO	World Health Organization

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