Protocol B7471009

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, THIRD-PARTY–UNBLINDED TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN PNEUMOCOCCAL VACCINE–NAÏVE ADULTS 60 YEARS OF AGE AND OLDER IN JAPAN, KOREA, AND TAIWAN

Statistical Analysis Plan (SAP)

Version: 2

Date: 27 Sep 2022

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APPENDICES

1. VERSION HISTORY

This SAP for Study B7471009 is based on the protocol, dated 13 Jan 2021.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 27 May 2021	Original: 13 Jan 2021	N/A	N/A
2 27 Sep 2022	N/A	Made updates to maintain consistency with the other 20vPnC adult programs.	• CCI • General – Made other minor edits/changes to be consistent with other 20vPnC studies, increase clarity, and correct minor errors that were present in original document.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471009. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. The impacts of COVID-19 will be assessed prior to the first planned analysis, and the SAP will be amended accordingly to account for these impacts, if needed.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary and secondary objective are described in Table 2. The estimands to evaluate the immunogenicity objectives for NI are based on evaluable populations (see Section 4 for definition). These estimands estimate the 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, 20vPnC/saline and 13vPnC/PPSV23, 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 AE start dates will be imputed according to Pfizer safety rules (Section 5.3). No other missing information will be imputed in the safety analysis.

Table 2. List of Primary, Secondary, CCI Objectives, Endpoints, and Estimands

Primary Safety Objective	Primary Safety Estimands	Primary Safety Endpoints
To describe the safety profile of 20vPnC.	In participants receiving at least 1 dose of investigational product and having safety follow-up after vaccination from each vaccine group: • The percentage of participants reporting prompted local reactions within 10 days after the first vaccination (20vPnC or 13vPnC) • The percentage of participants reporting prompted systemic events within 7 days after the first vaccination (20vPnC or 13vPnC) • The percentage of participants reporting AEs within 1 month after vaccination with 20vPnC or 13vPnC • The percentage of participants reporting SAEs within 1 month after vaccination with 20vPnC or 13vPnC	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) • AEs • SAEs
Primary Immunogenicity Objectives	**Primary Immunogenicity Estimands**	**Primary Immunogenicity Endpoints**
To demonstrate that the immune responses to the 13 serotypes in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 20vPnC are noninferior to the immune response induced by 13vPnC.	In participants in compliance with the key protocol criteria (evaluable participants): • For each of the 13 serotypes: GMR of serotype-specific OPA titers 1 month after 20vPnC to the serotype-specific OPA titers 1 month after 13vPnC	• Serotype-specific OPA titers
To demonstrate that the immune responses to the 7 additional serotypes in 20vPnC (8, 10A, 11A, 12F, 15B, 22F, and 33F) induced by 20vPnC are noninferior to the immune response induced by PPSV23.	In evaluable participants: For each of the 7 additional serotypes: GMR of serotype-specific OPA titers 1 month after 20vPnC to the serotype-specific OPA titers 1 month after PPSV23	• Serotype-specific OPA titers
Secondary Immunogenicity Objective	**Secondary Immunogenicity Estimand**	**Secondary Immunogenicity Endpoint**
To describe the immune responses to all 20 serotypes induced by 20vPnC.	In evaluable participants for each of the 20 serotypes: • Serotype-specific OPA GMTs 1 month after vaccination* in each vaccine group	• Serotype-specific OPA titers

Table 2. List of Primary, Secondary, CCI Objectives, Endpoints, and Estimands

	• GMFRs in serotype-specific OPA titers from before to 1 month after vaccination* in each vaccine group • Percentage of participants with ≥4-fold rise in serotype-specific OPA titers from before to 1 month after vaccination* in each vaccine group • Percentage of participants with serotype-specific OPA titers greater than or equal to the LLOQ 1 month after vaccination* in each vaccine group	
Secondary Safety Objective	**Secondary Safety Estimand**	**Secondary Safety Endpoint**
To describe the reactogenicity profile of PPSV23 following 13vPnC in Japanese participants (only for participants enrolled at Japan sites).	In participants receiving at least 1 dose of investigational product and having safety follow-up after vaccination from each vaccine group: • The percentage of participants reporting prompted local reactions within 10 days after the second vaccination (PPSV23 or saline) • The percentage of participants reporting prompted systemic events within 7 days after the second vaccination (PPSV23 or saline)	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain)

* Note: "1 month after vaccination" refers to 1 month after vaccination with 20vPnC (20vPnC/saline group), or 1 month after vaccination with 13vPnC for the 13 matched serotypes or PPSV23 for the 7 additional serotypes (13vPnC/PPSV23 group).

2.2. Study Design

This Phase 3, multicenter, randomized, double-blind study will be conducted at investigator sites in Japan, Korea, and Taiwan.

Approximately 1400 participants 60 years of age and older at enrollment will be randomized into 2 groups in a 1:1 ratio by center-based randomization, stratified by age (60 through 64 years of age and ≥65 years of age), and assigned to either the 20vPnC/saline group or the 13vPnC/PPSV23 group. Each participant will be randomized to receive either 20vPnC or 13vPnC (control vaccine) at Vaccination 1. Participants who receive 20vPnC at Vaccination 1 in the 20vPnC/saline group will receive saline at Vaccination 2. Participants who received 13vPnC at Vaccination 1 in the 13vPnC/PPSV23 group will receive PPSV23 at Vaccination 2.

On Day 1 (Visit 1), participants will be assessed for eligibility, have blood drawn for immunogenicity assessments, and receive 20vPnC or 13vPnC administered by blinded or unblinded site staff. Participants will be observed for at least 30 minutes after vaccination by blinded site staff, who will record AEs occurring during that time. Participants will also receive safety follow-up and e-diary instructions at the visit. Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) occurring within 7 days after vaccination and prompted local reactions (redness, swelling, and pain at the injection site) occurring at the 20vPnC or 13vPnC injection site within 10 days after vaccination will be collected daily in the e-diary. Use of antipyretic/pain medications will be collected daily in an e-diary for 7 days after vaccination.

Participants will return for Visit 2 (28 to 42 days after Visit 1), and information will be collected from the participants on AEs, SAEs, and e-diary follow-up (as needed). Blood will be drawn for immunogenicity assessments. Saline will be administered to participants who previously received 20vPnC, and PPSV23 will be administered to participants who previously received 13vPnC, by a third-party unblinded site staff member. Participants will be observed for at least 30 minutes after vaccination by blinded site staff, who will record AEs occurring during that time. Participants will also be reminded about safety follow-up. The control participants are receiving a schedule that has been studied previously with no safety concerns, but it is a research schedule and a specific request has been made by the PMDA to collect additional information in the Japanese population. For participants enrolled **at Japan sites**, prompted local reactions occurring at the saline or PPSV23 injection site within 10 days after vaccination and prompted systemic events occurring within 7 days after vaccination will be collected daily in the e-diary. Use of antipyretic/pain medications will be collected daily in an e-diary for 7 days after vaccination.

Participants will return for Visit 3 (28 to 42 days after Visit 2) and information will be collected from the participants on AEs and SAEs. Blood will be drawn for immunogenicity assessments.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

- Prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after vaccination.
- Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination.
- AEs within 1 month after vaccination with 20vPnC or 13vPnC.
- SAEs within 1 month after vaccination with 20vPnC or 13vPnC.

3.1.1.1. Local Reactions

The prompted local reactions that will be assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 10, where Day 1 is the day of vaccination at Visit 1 for all participants. CCI [redacted]

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21; an entry in the e-diary of 21 will denote measurements >20), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 3 below. Measuring device units will be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 3. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

Table 3. Grading Scales for Local Reactions

Local Reaction	Grade 1 Mild	Grade 2 Moderate	Grade 3[a] Severe	Grade 4[b]
Redness	5 to 10 measuring device units = >2.0 to 5.0 cm	11 to 20 measuring device units = >5.0 to 10.0 cm	>20 measuring device units = >10.0 cm	Necrosis or exfoliative dermatitis
Swelling	5 to 10 measuring device units = >2.0 to 5.0 cm	11 to 20 measuring device units = >5.0 to 10.0 cm	>20 measuring device units = >10.0 cm	Necrosis
Pain at injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity[c]	Emergency room visit or hospitalization for severe pain at the injection site

Abbreviation: CRF = case report form.
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.

a. Participants experiencing Grade 3 local reactions are required to contact the investigator site. In the event that the participant does not call, the investigator will call the participant.
b. Grade 4 assessments should be made by the investigator. Grade 4 reactions will not be collected in the e-diary but will be collected as AEs on the CRF. The severity of the local reaction should be graded using the AE severity grading scale.
c. Prevents daily activity, eg, results in missed days of work or is otherwise incapacitating.

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3.1.1.2. Systemic Events (Including Fever)

The systemic events that will be assessed and recorded in the diary are fever, headache, fatigue, muscle pain, and joint pain from Day 1 through Day 7, where Day 1 is the day of vaccination. [redacted]

The systemic events of fatigue, headache, muscle pain, and joint pain will be assessed by participants as mild, moderate, or severe according to the grading scale in Table 4. Participants will also be instructed to contact site staff or the investigator if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for severe headache, severe fatigue, severe muscle pain, or severe joint pain) within 7 days after vaccination. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

Table 4. Grading Scales for Systemic Events

	Grade 1 Mild	Grade 2 Moderate	Grade 3[a] Severe	Grade 4[b]
Fatigue (tiredness)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

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

a. Prevents daily activity, eg, results in missed days of work or school or is otherwise incapacitating; includes use of narcotics for analgesia.

b. Grade 4 assessments should be made by the investigator. Grade 4 events will not be collected in the e-diary but will be collected as AEs on the CRF. The severity of the systemic event should be graded using the AE severity grading scale.

Oral temperature will be collected in the evening daily for 7 days following vaccination at Visit 1 (Days 1 through 7, where Day 1 is the day of vaccination at Visit 1) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C. The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until the fever has resolved (1 day of temperature <38.0°C), in order to collect a stop date in the CRF. Temperature will be measured and recorded to 1 decimal place.

Fever will be grouped into ranges for the analysis according to Table 5 below.

Table 5. 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[a]

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

a. Participants reporting a fever >40.0°C will be prompted to contact the study site.

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3.1.1.4. Adverse Events

AEs will be categorized according to MedDRA terms. AEs will be collected from the signing of the ICD through Visit 3 (approximately 1 month after Visit 2). The primary-endpoint AEs within 1 month after vaccination with 20vPnC or 13vPnC will be summarized by system organ class and preferred term on a participant level.

This primary endpoint will be supported by summaries and listings of related AEs, severe AEs, and immediate AEs (within the first 30 minutes after vaccination at Visit 1).

AE reporting will be based on the specific reporting period. Standard algorithms for handling missing AE dates and missing AE severity will be applied as described in the Pfizer vaccine data standard rules.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers:

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's safety review plan. No Tier 1 events have been identified to date for 20vPnC.

- Tier 2 events: These are events 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 with the AE term in at least 1 vaccine group.

- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

3.1.1.5. Serious Adverse Events

SAEs will be categorized according to MedDRA terms. SAEs will be collected from the signing of the ICD through Visit 3 (approximately 1 month after Visit 2).

3.1.2. Primary Immunogenicity Endpoint

- Serotype-specific OPA titers 1 month after vaccination.

OPA titers for the 20 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) will be determined for all participants prior to vaccination at Visit 1 and at Visit 2 (approximately 1 month after Visit 1). OPA titers will be

determined only for the 7 additional serotypes at Visit 3 (approximately 1 month after Vaccination 2).

OPA titers above the LLOQ are considered accurate and their quantitated values will be reported. OPA titers below the corresponding LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. Missing assay results will not be imputed.

3.2. Secondary Endpoints

3.2.1. Secondary Safety Endpoint (Participants at Japan Sites Only)

The same summaries as specified in Sections 3.1.1.1 and 3.1.1.2 will be provided.

- Prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after the second vaccination (PPSV23 following 13vPnC or saline following 20vPnC)
- Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after the second vaccination (PPSV23 following 13vPnC or saline following 20vPnC)

3.2.2. Secondary Immunogenicity Endpoint

- Serotype-specific OPA titers 1 month after vaccination
- Fold rises in OPA titers from before vaccination to 1 month after vaccination
- Classification of fold rise in OPA titers from before vaccination to 1 month after vaccination as a ≥4-fold rise
- Classification of titers as ≥ LLOQ at 1 month after vaccination

3.3. Other Endpoints

Not applicable.

3.4. Baseline and Other Variables

Day 1 is defined as the day of vaccination. Measurements or samples collected prior to vaccination on Day 1 are considered the baseline data for the assessments.

The following variables will be summarized as part of the baseline characteristics:

- Demographics
- Medical history
- Smoking history

Other variables to be summarized or listed include the following:

- E-diary transmission
- Nonstudy vaccines
- Concomitant medications that the participant is currently taking for medical conditions at enrollment
- Concomitant medications to treat SAEs

3.4.1. Demographics, Smoking History, and Medical History

The demographic variables are age at vaccination at Visit 1 (in years), age group (60 to 64 years or 65 years and older), sex (male or female), race (Black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, White, or not reported), racial designation (Japanese, Korean, Taiwanese, or Other), country (Japan, Korea, or Taiwan), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, or not reported). In cases where more than 1 category is selected for race, the participant will be counted under the category "multiracial" for analysis.

Age in years at the first vaccination will be derived based on the participant's birthday. For example, if the vaccination date is 1 day before the participant's 65th birthday, the participant is considered to be 64 years old. For participants who are randomized but not vaccinated, the randomization date will be used in place of the date of the first vaccination for age calculation. If the randomization date is also missing, then the informed consent date will be used for age calculation.

Smoking history will be recorded as "current smoker," "ex-smoker," and "never smoked." Start and stop dates for an ex-smoker and start date for a current smoker will be recorded on the CRF. Elapsed time since an ex-smoker stopped smoking will be summarized in years and derived as (Vaccination 1 date – stop date + 1)/365.25. Elapsed time since a current smoker started smoking will be derived as (Vaccination 1 date - start date + 1)/365.25. The midpoint value will be used to impute a partial date to the full date.

Demographic and disposition tables will be categorized by vaccine group. In addition, separate demographic tables by enrollment country and age group (60 through 64 years of age or 65 years of age and above) will be provided.

Medical history will be categorized according to MedDRA. Significant findings from any physical examination performed at baseline will also be collected on the medical history page of the CRF and summarized with the medical history.

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CCI [redacted]

3.4.3. Nonstudy Vaccines and Concomitant Medications

The name and date of administration for any nonstudy vaccinations received from the time of signing of the ICD to the final visit will be collected and recorded in the CRF. Details of any medications that the participant is currently taking for medical conditions at enrollment will be recorded in the CRF. Medications taken to treat SAEs from the time of signing of the ICD to the final visit will also be collected. Nonstudy vaccines and concomitant medications will be coded using the WHODD.

3.5. Safety Endpoints

Not applicable.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety and immunogenicity results in the table below. For the specified criteria in each population definition that are not associated with unblinded information (randomized or actual received vaccination), data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database for the specified analysis, and the classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable 13-matched immunogenicity	This population was the primary analysis population for immunogenicity results of the 13 matched serotypes. This population generally includes any randomized participant who: • is eligible based on inclusion and exclusion criteria • receives the first vaccine (20vPnC or 13vPnC) as randomized • has the Visit 2 blood collection within 27 to 49 days after Vaccination 1 • has at least 1 valid OPA titer for any of the 13 matched serotypes at Visit 2 • has no other major protocol deviations as determined by the clinician.

Population	Description
Evaluable 7-additional immunogenicity	This population is the primary analysis population for immunogenicity results of the 7 additional serotypes. This population generally includes any randomized participant who: • is eligible based on inclusion and exclusion criteria • receives the assigned investigational products at Visit 1 (20vPnC) for the 20vPnC/saline group or receives the assigned investigational products at both Visit 1 and Visit 2 (13vPnC and PPSV23) for the 13vPnC/PPSV23 group • has either the Visit 2 blood collection within 27 to 49 days after Vaccination 1 (20vPnC) for the 20vPnC/saline group or the Visit 3 blood collection within 27 to 49 days after Vaccination 2 (PPSV23) for the 13vPnC/PPSV23 group • has at least 1 valid OPA titer for any of the 7 additional serotypes at either Visit 2 for the 20vPnC/saline group or Visit 3 for the 13vPnC/PPSV23 group • has no other major protocol deviations as determined by the clinician.
CCI [redacted]	[redacted]
Safety	All participants who receive at least 1 dose of the investigational product.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity population.

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

All safety analyses will be based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually receive.

Analyses of reactogenicity endpoints are based on a subset of the safety population that includes participants with any e-diary data reported after the specified vaccination.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Hypothesis testing will be performed to assess noninferiority, comparing the 20vPnC/saline vaccine group against the 13vPnC/PPSV23 vaccine group for each of the 20 serotype-specific OPA titers.

A 2-fold margin will be used for each of the noninferiority hypothesis test.

5.1.1. Hypothesis Testing

Hypothesis testing will be performed to assess noninferiority by comparing the serotype-specific OPA titers of the 20vPnC/saline group to those from the 13vPnC/PPSV23 group. The null hypothesis for each serotype-specific OPA titer is:

$$H_0: \ln(\mu_A) - \ln(\mu_B) \leq \ln(0.5)$$

where $\ln(0.5)$ corresponds to a 2-fold margin for the assessment of noninferiority.

- $\ln(\mu_A)$ is the natural log of the serotype-specific OPA GMT 1 month after 20vPnC administration for the 20vPnC/saline group.

- $\ln(\mu_B)$ is the natural log of the serotype-specific OPA GMT 1 month after 13vPnC administration for the 13vPnC/PPSV23 group when the endpoint is the serotype-specific OPA GMT from 1 of the shared 13 serotypes in 13vPnC, or,

- $\ln(\mu_B)$ is the natural log of the serotype-specific OPA GMT 1 month after PPSV23 administration for the 13vPnC/PPSV23 group when the endpoint is the serotype-specific OPA GMT from 1 of the 7 additional serotypes.

Noninferiority for serotype-specific OPA titers will be formally evaluated by a 2-sided 95% CI for the ratio of serotype-specific OPA GMTs (the 20vPnC/saline group to the 13vPnC/PPSV23 group) with results from 1 month after vaccination with 20vPnC (Visit 2) and 1 month after vaccination with 13vPnC (Visit 2) for the 13 matched serotypes. For the 7 additional serotypes, the GMR will be calculated for the ratio of serotype-specific OPA GMTs from the 20vPnC/saline group at Visit 2 to that from the 13vPnC/PPSV23 group at Visit 3. Noninferiority for a serotype will be declared if the lower bound of the 2-sided 95% CI for the ratio of $GMT_{20vPnC/saline}$ to $GMT_{13vPnC/PPSV23}$ for that serotype is greater than 0.5 (2-fold criterion).

5.2. General Methods

Time points for local reactions and systemic events refer to data within 10 and 7 days after vaccination at Visit 1 and Visit 2 (for participants at Japan sites only), respectively.

Prompted local reactions, prompted systemic events, and AEs will be summarized after each vaccination at Visit 1 and Visit 2 by vaccine group.

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level.

5.2.1. Analyses for Binary Endpoints

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CI where applicable.

The exact 95% CI for binary endpoints for each vaccine group will be computed using the F distribution (Clopper-Pearson).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[2]

The 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

5.2.2. Analyses for Continuous Endpoints

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

Continuous immunogenicity outcomes of serotype-specific OPA titers will be analyzed on the natural log scale, and the results will be reported on the original scale after back transformation.

5.2.2.1. Geometric Mean Titers

For immunogenicity results of serotype-specific OPA titers, the geometric means will be computed along with associated 95% CIs. The GMTs and associated 2-sided 95% CIs will be calculated as the means and CIs of the assay results on the natural logarithmic scale based on the t-distribution, and then exponentiating the results.

5.2.2.2. Geometric Mean Ratios

The OPA serotype-specific antibody titer ratios (GMRs) will be calculated for each of the noninferiority assessments as:

The GMT ratio of 20vPnC/saline to 13vPnC/PPSV23:

- ratio of the GMT from the 20vPnC/saline group to that from the 13vPnC/PPSV23 group at Visit 2 for the 13 matched serotypes.

- ratio of the GMT from the 20vPnC/saline group at Visit 2 to that from the 13vPnC/PPSV23 group at Visit 3 for the 7 additional serotypes.

Details regarding the derivation of GMRs are provided below in Table 6.

Table 6. Derivation of Serotype-Specific OPA GMRs at 1 Month After Vaccination

Comparison	Analysis Population	Serotypes	Numerator	Denominator
Between–vaccine group comparison	Evaluable 13-matched immunogenicity population	13 matching serotypes	20vPnC/saline group at Visit 2	13vPnC/PPSV23 group at Visit 2
	Evaluable 7-additional immunogenicity population	7 additional serotypes	20vPnC/saline group at Visit 2	13vPnC/PPSV23 group at Visit 3

Abbreviations: GMR = geometric mean ratio; OPA = opsonophagocytic activity.

For each comparison above, there will be 2 approaches to calculating the GMR and CI for each serotype:

Model-Based GMR

The primary approach will be based on a linear regression model. Specifically,

- For the comparison of OPA results, the following terms will be included in the regression model: corresponding baseline OPA titer, age, sex (male or female), country (Japan, Korea, or Taiwan), smoking status (current smoker, ex-smoker, or never smoked), and vaccine group.

The difference between these LS means of OPA titers on the natural log scale and associated CI estimated from the linear regression model will be exponentiated to obtain the GMR and CI.

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A 2-sided 95% CI will be used for the noninferiority comparison of the 20vPnC/saline group to the 13vPnC/PPSV23 group.

5.2.2.3. Geometric Mean Fold Rises

The GMFRs will be calculated as the mean of the difference of logarithmically-transformed assay results (later minus earlier) and exponentiating back to the original units. The associated 2-sided 95% CIs will be computed by exponentiating the CIs using Student's t-distribution for the mean difference on the natural log scale.

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5.3. Methods to Manage Missing Data

A partial AE start date (missing day, missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the vaccination date(s) from the same participant, following the Pfizer standard of handling incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection. No additional imputation will be applied unless stated otherwise (see Section 3).

The LLOQ for each assay will be provided by Vaccine Research & Development as part of the electronic data transfer or within the Clinical Testing Completion Memo prior to any statistical analysis of immunogenicity data. Assay results above the LLOQ will be reported, and values below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis.

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6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions

6.1.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after the first vaccination (20vPnC or 13vPnC) (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 10 days after the first vaccination.

- Analysis methodology: Descriptive statistics. The percentage (%), and the corresponding 95% Clopper-Pearson CI will be presented by vaccine group (20vPnC/saline [Vaccination 1], 13vPnC/PPSV23 [Vaccination 1]). The between-group difference (20vPnC/saline [Vaccination 1] - 13vPnC/PPSV23 [Vaccination 1]) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method[1] (Section 5.2.1) for each reaction.

- Intercurrent events and missing data: Missing values will not be imputed.

- Reporting results: Count and percentage of participants with the indicated endpoint and the associated 2-sided 95% Clopper-Pearson CI for each and any local reaction in each vaccine group will be presented by maximum severity level. Between-group differences in these percentages and their 2-sided 95% CIs will also be provided.

CCI [redacted]

6.1.1.2. Prompted Systemic Events

6.1.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after the first vaccination (20vPnC or 13vPnC) (Section 2.1).

- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after vaccination after the first vaccination.
- Analysis methodology: Descriptive statistics. The percentage (%), and the corresponding 95% Clopper-Pearson CI will be presented by vaccine group (20vPnC/saline [Vaccination 1], 13vPnC/PPSV23 [Vaccination 1]). The between-group difference (20vPnC/saline [Vaccination 1] - 13vPnC/PPSV23 [Vaccination 1]) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method[1] (Section 5.2.1) for each reaction.
- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Count and percentage of participants with the indicated endpoint and the associated 2-sided 95% CI for each and any systemic event in each vaccine group will be presented by maximum severity across severity levels. Between-group differences in these percentages and their 2-sided 95% CIs will also be provided.

CCI [redacted]

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimand: The percentage of participants reporting AEs within 1 month after vaccination with 20vPnC or 13vPnC.

- Analysis set: Safety population (Section 4).
- Analysis time point: Within 1 month after vaccination.
- Analysis methodology: 3-Tiered approach as described in Section 5.2.1.
- Intercurrent events and missing data: No missing values will be imputed except for partial AE start dates (Section 5.3).
- Reporting results: For all 3 tiers, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% Clopper-Pearson CI for participants reporting any AE, by each system organ class and each preferred term within system organ class, will be presented by vaccine group.

  In addition, for AEs classified as Tier 2 events, the differences in percentages (20vPnC/saline - 13vPnC/PPSV) and associated 2-sided 95% CIs using the Miettinen and Nurminen method will be provided.

  Further, for Tier 1 events, if any are identified, the difference in percentages, the associated 2-sided 95% CI for the risk difference, and the asymptotic p-values will also be provided.

If any nonserious AEs are reported to occur before vaccination at Visit 1, they will not be included in the summary but will be included in the AE listings.

CCI [redacted]

6.1.1.4. Serious Adverse Events

6.1.1.4.1. Main Analyses

- Estimand: The percentage of participants reporting SAEs within 1 month after vaccination with 20vPnC or 13vPnC.
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 1 month after vaccination.

- Analysis methodology: Descriptive statistics.

- Intercurrent events and missing data: No missing values will be imputed except for partial SAE start dates (see Section 5.3).

- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%) and the corresponding 95% Clopper-Pearson CI for participants reporting any SAE, by each system organ class and each preferred term within system organ class, will be presented by vaccine group. There will be a listing of all AEs, including SAEs, and a separate listing of SAEs only.

CCI [redacted]

[redacted]

6.1.2. Primary Immunogenicity Endpoint

The ordering of the pneumococcal serotypes in summaries will be as follows:

- 13vPnC serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F; and

- Additional 7 serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F.

6.1.2.1. Main Analysis

- Estimand:

  - For each of the 13 serotypes: GMR of serotype-specific OPA titers 1 month after 20vPnC to the serotype-specific OPA titers 1 month after 13vPnC.

  - For each of the 7 additional serotypes: GMR of serotype-specific OPA titers 1 month after 20vPnC to the serotype-specific OPA titers 1 month after PPSV23.

- Analysis set: Evaluable 13-matched immunogenicity (13vPnC serotypes), evaluable 7-additional immunogenicity population (7 additional serotypes), CCI [redacted]

- Analysis time point: 1 Month after administration of 20vPnC (Visit 2), 1 month after administration of 13vPnC (Visit 2), or 1 month after administration of PPSV23 (Visit 3).

- Analysis methodology: Linear regression model with terms for corresponding baseline OPA titer, age, sex (male or female), country (Japan, Korea, or Taiwan), smoking status (current smoker, ex-smoker, or never smoked), and vaccine group (20vPnC/saline group or 13vPnC/PPSV23 group).

- Reporting results: The LS GMTs and associated 95% CIs for serotype-specific OPA titers from each vaccine group, as well as the model-based OPA GMRs with their associated 95% CIs, will be summarized separately for the 13 matching pneumococcal serotypes and for the 7 additional serotypes.

If participants' racial designation is different from their enrollment country, the factor for linear regression is based on the enrollment country.

Reporting results:

The LS GMTs and associated 95% CIs for serotype-specific OPA titers from each vaccine group, as well as the model-based OPA GMRs with their associated 95% CIs, will be summarized separately for the 13 matching pneumococcal serotypes and for the 7 additional serotypes.

Figures:

A forest plot of GMRs with 95% CIs for all 20 serotypes, with a vertical reference line corresponding to GMR=0.5, will be presented.

CCI

- CCI [redacted]

[redacted]

[redacted]

6.2. Secondary Endpoints

6.2.1. Secondary Safety Endpoints (For Participants Enrolled at Japan Site Only)

6.2.1.1. Local Reactions

6.2.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after the second vaccination (PPSV23 or saline) (Section 2.1).
- Analysis set: Vaccinated participants receiving PPPSV23 in the 13vPnC/PPSV23 group or saline in the 20vPnC/saline group in the safety population (Section 4).
- Analysis time point: Within 10 days after vaccination with PPPSV23 in the 13vPnC/PPSV23 group or saline in the 20vPnC/saline group.
- Analysis methodology: The percentage (%) and the corresponding 95% Clopper-Pearson CI will be presented.
- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Count and percentage of participants with the indicated endpoint and the associated 2-sided 95% CI for each and any local reaction after each dose in each vaccine group will be presented by maximum severity across severity levels.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

6.2.1.2. Systemic Events

- Estimand: The percentage of participants reporting prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after the second vaccination (PPSV23 or saline) (Section 2.1).
- Analysis set: Vaccinated participants receiving PPPSV23 in the 13vPnC/PPSV23 group or saline in the 20vPnC/saline group in the safety population (Section 4).
- Analysis time point: Within 7 days after vaccination with PPSV23 in the 13vPnC/PPSV23 group or saline in the 20vPnC/saline group.
- Analysis methodology: The percentage (%) and the corresponding 95% Clopper-Pearson CI will be presented by vaccine group.
- Intercurrent events and missing data: Missing values will not be imputed.
- Reporting results: Count and percentage of participants with the indicated endpoint and the associated 2-sided 95% CI for each and any local reaction after each dose in each vaccine group will be presented by maximum severity across severity levels.

CCI [redacted]

CCI

[redacted]

6.2.2. Secondary Immunogenicity Endpoints

6.2.2.1. Main Analysis

- Estimand: Serotype-specific OPA GMTs 1 month after vaccination in each vaccine group.
- Analysis set: Evaluable 13-matched immunogenicity (13vPnC serotypes), evaluable 7-additional immunogenicity population (7 additional serotypes), CCI [redacted]
- Analysis time point: 1 month after administration of 20vPnC (Visit 2), 1 month after administration of 13vPnC (Visit 2), or 1 month after administration of PPSV23 (Visit 3).
- Analysis methodology: OPA GMTs and the 2-sided 95% CIs for each vaccine group based on the Student's t-distribution (Section 5.2.2.1).
- Reporting results: Observed GMTs and 95% CIs for serotype-specific OPA titers will be presented for each vaccine group, both before vaccination and 1 month after vaccination.

Figures:

Bar charts for observed OPA GMTs and corresponding 95% CIs for the 13 serotypes will be plotted at before Vaccination 1 and 1 month after Vaccination 1 for each vaccine group. Similar plots will be generated for before Vaccination 1 and 1 month after vaccination (Vaccination 1 for the 20vPnC/saline group and Vaccination 2 for the 13vPnC/PPSV23 group) for the 7 additional serotypes.

6.2.2.2. Fold Changes in Serotype-specific OPA Titers

- Estimand: GMFRs in serotype-specific OPA titers from before to 1 month after vaccination in each vaccine group.
- Analysis set: Evaluable 13-matched immunogenicity (13vPnC serotypes), evaluable 7-additional immunogenicity population (7 additional serotypes), CCI [redacted]
- Analysis time point: Before vaccination (Visit 1) to 1 month after vaccination with 20vPnC or 13vPnC (Visit 2) for the 13 matched serotypes, and 1 month after vaccination with PPSV23 (Visit 3) for the 7 additional serotypes.

- Reporting results: The number of participants (n), OPA GMFRs, and associated 95% CIs from before vaccination to 1 month after vaccination will be summarized by vaccine group. For the 13 matching serotypes, the GMFR will be the ratio of GMTs at Visit 2 to Visit 1 for each vaccine group. The GMFRs for the 7 additional serotypes will be the ratio of GMTs at Visit 2 to Visit 1 for the 20vPnC/saline group, and the ratio of GMTs at Visit 3 to Visit 1 for the 13vPnC/PPSV23 group.

6.2.2.3. Participants With a ≥4-Fold Rise in Serotype-Specific OPA Titers From Before to 1 Month After Vaccination

- Estimand: Percentage of participants with ≥4-fold rise in serotype-specific OPA titers from before to 1 month after vaccination in each vaccine group.

- Analysis set: Evaluable 13-matched immunogenicity (13vPnC serotypes), evaluable 7-additional immunogenicity population (7 additional serotypes), CCI [redacted]

- Analysis time point: Before vaccination (Visit 1) to 1 month after vaccination with 20vPnC (Visit 2) for all 20 serotypes or 13vPnC (Visit 2) for the 13 matched serotypes, and 1 month after vaccination with PPSV23 (Visit 3) for the 7 additional serotypes.

- Reporting results: The proportion of participants with a ≥4-fold rise and associated 95% CI from Visit 1 to Visit 2 for the 13 matching serotypes by vaccine group will be summarized. The proportion of participants for the 7 additional serotypes will be the proportion of participants with a ≥4-fold rise from Visit 1 to Visit 2 for the 20vPnC/saline group and from Visit 1 to Visit 3 for the 13vPnC/PPSV23 group. The number of participants (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 95% Clopper-Pearson CI will be presented by vaccine group.

6.2.2.4. Participants With OPA Titers ≥LLOQ

- Estimand: Percentage of participants with ≥LLOQ in serotype-specific OPA titers 1 month after vaccination in each vaccine group.

- Analysis set: Evaluable 13-matched immunogenicity (13vPnC serotypes), evaluable 7-additional immunogenicity population (7 additional serotypes), CCI [redacted]

- Analysis time point: 1 Month after administration of 20vPnC (Visit 2), 1 month after administration of 13vPnC (Visit 2), or 1 month after administration of PPSV23 (Visit 3).

- Reporting results: The proportions of participants with serotype-specific OPA titers ≥LLOQ and associated 95% CIs will be calculated for the time point before vaccination (Visit 1) and 1 month after vaccination with 20vPnC or 13vPnC (Visit 2), by vaccine, and 1 month after vaccination with PPSV23 (Visit 3). For the 13 matching serotypes, the proportion of participants with OPA titers ≥LLOQ will be calculated for Visit 1 and Visit 2 for all groups. For the 7 additional serotypes, the proportion of participants with OPA titers ≥LLOQ will be calculated for Visits 1 and 2 for the 20vPnC/saline group, and Visits 1 and 3 for the 13vPnC/PPSV23 group. The number of participants (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 95% Clopper-Pearson CI will be presented by vaccine group.

6.3. Other Endpoints

Not applicable.

CCI

- CCI [redacted]

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age at vaccination at Visit 1 (in years), age group (60 through 64 years of age and ≥65 years of age), sex, race, racial designation, country, and ethnicity will be summarized by vaccine group for all participants in the safety population and evaluable immunogenicity populations. These characteristics will also be summarized by country (Japan, Korea, and Taiwan).

The proportions of participants reporting as "current smoker," "ex-smoker," and "never smoked" will be summarized. Descriptive statistics for elapsed time since a current smoker started smoking and for elapsed time since an ex-smoker stopped smoking will be provided.

The proportion of participants who are identified with underlying medical conditions or risk factors that increase the risk of pneumococcal infection will be tabulated separately by vaccine group.

6.5.1.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to MedDRA. The number and percentage of participants with an assigned vaccine having at least 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized by vaccine group for the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received vaccination(s) at Visit 1 and at Visit 2; who completed participation through Visit 3; who completed the study; and who withdrew from the study, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment). The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately, along with the reasons for exclusion, by vaccine group.

6.5.2.2. Blood Samples for Assay

The number and percentage of randomized participants providing blood samples within and outside of protocol-prespecified time frames, at each time point, will be tabulated by vaccine group.

CCI [redacted]

6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

A listing of participants showing the randomized vaccine and the vaccine actually received (20vPnC or 13vPnC) or the randomized vaccine group and the vaccines actually received (20vPnC/saline or 13vPnC/PPSV23) will be presented for each vaccine group.

6.5.4. Nonstudy Vaccinations and Concomitant Medications Used to Treat SAEs

Nonstudy vaccines received, medications taken to treat SAEs during the study, and medications taken at the time of enrollment will be listed.

Medications taken at the time of enrollment will be summarized for the participants in the safety population.

6.6. Safety Summaries and Analyses

Not applicable.

7. INTERIM ANALYSES

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

7.3. Analysis Timings

Statistical analyses will be carried out when the final data for the specified analyses are available.

8. REFERENCES

1. Collett D. Statistical inference for binary data. Chapter 2. In: Modelling binary data. London, England: Chapman & Hall; 1991:17-42.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
13vPnC	13-valent pneumococcal conjugate vaccine
20vPnC	20-valent pneumococcal conjugate vaccine
AE	adverse event
BLQ	below the limit of quantitation
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IWR	interactive Webbased response
LLOQ	lower limit of quantitation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NI	noninferiority
OPA	opsonophagocytic activity
PMDA	Pharmaceuticals and Medical Devices Agency
PPSV23	23-valent pneumococcal polysaccharide vaccine
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
WHODD	World Health Organization Drug Dictionary

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