**Protocol B7471004**

# A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (20vPnC) WHEN COADMINISTERED WITH SEASONAL INACTIVATED INFLUENZA VACCINE (SIIV) IN ADULTS ≥65 YEARS OF AGE

**Statistical Analysis Plan**
**(SAP)**

**Version:** 1

**Date:** 27 Oct 2020

[redacted]



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**APPENDICES**

# 1. VERSION HISTORY

**Table 1. Summary of Changes**

| Version/ Date | Associated Protocol Amendment | Rationale | Specific Changes |
|---|---|---|---|
| 1<br>27 Oct 2020 | Original protocol<br>15 Jun 2020 | N/A | N/A |

# 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471004. 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, secondary, CCI [redacted] 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, (SIIV+20vPnC)/saline and (SIIV+saline)/20vPnC, 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 [redacted] Objectives, Endpoints, and Estimands**

| Primary Safety Objective | Primary Safety Estimands | Primary Safety Endpoints |
|---|---|---|
| • To describe the safety profile of 20vPnC when coadministered with or 1 month after SIIV | In participants receiving 1 dose of 20vPnC or SIIV or saline and having safety follow-up after vaccination from each vaccine group:<br>• The percentage of participants reporting prompted local reactions within 10 days after each vaccination | • Prompted local reactions (redness, swelling, and pain at the injection site)<br>• Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain)<br>• AEs<br>• SAEs<br>• NDCMCs |

**Table 2. List of Primary, Secondary, CCI [redacted] Endpoints, and Estimands**

| | | |
|---|---|---|
| | • The percentage of participants reporting prompted systemic events within 7 days after each vaccination<br>• The percentage of participants reporting AEs within 1 month after each vaccination<br>• The percentage of participants reporting SAEs up to 6 months after the last vaccination<br>• The percentage of participants reporting NDCMCs up to 6 months after the last vaccination | |
| **Primary Pneumococcal Immunogenicity Objective** | **Primary Pneumococcal Immunogenicity Estimand** | **Primary Pneumococcal Immunogenicity Endpoint** |
| • To demonstrate that the OPA GMTs elicited by 20vPnC when coadministered with SIIV (20vPnC+SIIV) are noninferior to those elicited by 20vPnC when administered 1 month after SIIV | In participants in compliance with the key protocol criteria (evaluable participants):<br>• GMR of the serotype-specific OPA titers 1 month after vaccination with 20vPnC from the coadministration group to the serotype-specific OPA titers 1 month after vaccination with 20vPnC from the separate-administration group | • Pneumococcal serotype-specific OPA titers |
| **Primary SIIV Immunogenicity Objective** | **Primary SIIV Immunogenicity Estimand** | **Primary SIIV Immunogenicity Endpoint** |
| • To demonstrate that the HAI GMTs elicited by SIIV when coadministered with 20vPnC (20vPnC+SIIV) are noninferior to those elicited by SIIV alone | In evaluable participants:<br>• GMR of the strain-specific HAI titers 1 month after vaccination with SIIV from the coadministration group to the corresponding strain from the separate-administration group | • Strain-specific HAI titers |
| **Secondary Pneumococcal Immunogenicity Objective** | **Secondary Pneumococcal Immunogenicity Estimands** | **Secondary Pneumococcal Immunogenicity Endpoint** |
| • To describe the fold rises of immune responses to 20vPnC when coadministered with or 1 month after SIIV | In evaluable participants from each vaccine group:<br>• GMFR in serotype-specific OPA titers from before vaccination to 1 month after vaccination<br>• The percentage of participants with a ≥4-fold rise in serotype-specific OPA titers from before vaccination to 1 month after vaccination | • Pneumococcal serotype-specific OPA titers |

**Table 2. List of Primary, Secondary CCI [redacted] Endpoints, and Estimands**

| Secondary SIIV Immunogenicity Objective | Secondary SIIV Immunogenicity Estimand | Secondary SIIV Immunogenicity Endpoint |
|---|---|---|
| • To describe the fold rises of immune responses to SIIV when coadministered with 20vPnC or administered alone | In evaluable participants from each vaccine group:<br>• GMFR in strain-specific HAI titers from before vaccination to 1 month after vaccination | • Strain-specific HAI titers |
| CCI [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] s |

## 2.2. Study Design

This Phase 3, multicenter, randomized, double-blind study will be conducted at investigator sites in the United States.

Approximately 1780 healthy adults ≥65 years of age will be stratified by prior pneumococcal vaccine status (no previous pneumococcal vaccine [naïve], receipt of at least 1 dose of PPSV23 only, receipt of at least 1 dose of 13vPnC only, or receipt of at least 1 dose each of PPSV23 and 13vPnC) and randomized in a 1:1 ratio to 1 of 2 groups by center-based randomization. The coadministration group ([SIIV+20vPnC]/saline) will receive SIIV and 20vPnC at the same visit (Visit 1), followed 1 month later by administration of saline (Visit 2). The separate-administration group ([SIIV+saline]/20vPnC) will receive SIIV and saline at Visit 1, followed 1 month later with 20vPnC administered at Visit 2.

Blood will be collected at Visit 1 (prior to vaccination); at Visit 2 (prior to vaccination, 1 month after Visit 1); and at Visit 3 (1 month after Visit 2), to assess immunogenicity. Participants will be observed for 30 minutes after each vaccination and any reactions occurring during that time will be recorded as AEs.

Prompted local reactions (redness, swelling, and pain at the injection site) occurring at the 20vPnC/saline injection site within 10 days after vaccination (where Day 1 is the day of vaccination) and prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) and use of antipyretic/pain medications occurring within 7 days after vaccination (where Day 1 is the day of vaccination) will be collected via an e-diary after each vaccination visit (Visit 1 and Visit 2).

AEs will be collected from the signing of the ICD through Visit 3 (approximately 1 month after Visit 2). SAEs and NDCMCs will be collected from the signing of the ICD through 6 months after Visit 2.

## 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 each vaccination
- Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after each vaccination
- AEs within 1 month after each vaccination
- SAEs up to 6 months after the last vaccination
- NDCMCs up to 6 months after the last vaccination

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***Severity and Maximum Severity***

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21 and >21), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 4. 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 4.

**Table 4. Grading Scales for Local Reactions**

| Local Reaction | GRADE 1 Mild | GRADE 2 Moderate | GRADE 3 Severe | GRADE 4[a] |
|---|---|---|---|---|
| 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[b] | 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. 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. The severity of the local reaction should be graded using the AE severity grading scale.
b. Prevents daily activity, eg, results in missed days of work or is otherwise incapacitating.

For each local reaction after each vaccination, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 10, where Day 1 is the day of vaccination) as follows:

> maximum severity grade = highest grade (maximum severity) within 10 days after vaccination (Day 1 through Day 10) among severity grades reported for that local reaction in the e-diary.

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The systemic events of headache, fatigue, muscle pain, and joint pain will be assessed by participants as mild, moderate, or severe according to the grading scale in Table 5. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

**Table 5. Grading Scales for Systemic Events**

| | Mild Grade 1 | Moderate Grade 2 | Severe Grade 3[a] | 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 |

Abbreviation: CRF = case report form.

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

b. Grade 4 assessment should be made by the investigator; Grade 4 systemic 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 each vaccination (Day 1 through Day 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 oral temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature <100.4°F [<38.0°C]) in order to collect a stop date in the CRF. Temperature will be measured and recorded to 1 decimal place.

Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Fever will be grouped into ranges for the analysis according to Table 6.

**Table 6. 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 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 each vaccination 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 (start time is within the first 30 minutes after vaccination).

AE reporting will be based on the specific reporting period. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

A 3-tier approach will be used to summarize AEs within 1 month after each vaccination. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.1.1.3.1).

- 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 "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.

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

### 3.1.1.5. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

SAEs and NDCMCs will be categorized according to MedDRA terms. NDCMCs and SAEs will be collected from the signing of the ICD through the end of the study.

### 3.1.2. Primary Pneumococcal Immunogenicity Endpoint

- Pneumococcal serotype-specific OPA titers 1 month after vaccination with 20vPnC.

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' sera collected at Visit 1 (prior to administration of SIIV and blinded vaccine), Visit 2 (1 month after administration of vaccines at Visit 1, and prior to blinded vaccine at Visit 2), and Visit 3 (1 month after vaccination at Visit 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.

### 3.1.3. Primary SIIV Immunogenicity Endpoint

- Strain-specific HAI titers 1 month after vaccination with SIIV

HAI titers to the influenza strains (A/H1N1, A/H3N2, B/Victoria, and B/Phuket) in the SIIV administered will be determined on sera collected at Visit 1 (prior to administration of SIIV and blinded vaccine) and Visit 2 (1 month after SIIV administration at Visit 1).

HAI titers above the LLOQ are considered accurate and their quantitated values will be reported. HAI 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 Pneumococcal Immunogenicity Endpoints

- Pneumococcal serotype-specific OPA titers and fold rises in OPA titers from before vaccination to 1 month after vaccination with 20vPnC
    - The fold rises will be the ratio of OPA titers at Visit 2 to Visit 1 for the (SIIV+20vPnC)/saline group and the ratio of OPA titers at Visit 3 to Visit 1 for the (SIIV+saline)/20vPnC group.
- Classification of fold rise in OPA titers from before vaccination to 1 month after vaccination with 20vPnC as a ≥4-fold rise

### 3.2.2. Secondary SIIV Immunogenicity Endpoint

- Strain-specific HAI titers and fold rises in HAI titers from before vaccination to 1 month after vaccination with SIIV
    - The fold rises will be the ratio of HAI titers at Visit 2 to Visit 1 for both vaccine groups.

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### 3.4. Baseline and Other Variables

Day 1 is defined as the day of vaccination at Visit 1. 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
- CCI
- 

Other variables to be summarized include the following:

- CCI
- Nonstudy vaccines
- Concomitant medications to treat SAEs or NDCMCs

### 3.4.1. Demographics, CCI [redacted] Medical History, CCI [redacted] CCI [redacted]

The demographic variables are age at vaccination at Visit 1 (in years), sex (male or female), race (black or African American, American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, white, multiracial, and not reported), and ethnicity (Hispanic or Latino or of Spanish origin, not Hispanic or Latino or of Spanish origin, not reported). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Age at the first vaccination in years will be derived based on the participant's birthday. For example, if the vaccination date is 1 day before the participant's 70th birthday, the participant is considered to be 69 years old. For participants who were 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.

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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 medical history.

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[redacted]

[redacted]

### 3.4.3. Nonstudy Vaccines and Concomitant Medications

The name and date of administration of CCI [redacted] all nonstudy vaccinations received from the time of signing of the ICD to Visit 3, will be summarized. Concomitant medications will be recorded only if they were used to treat SAEs or NDCMCs from the time of signing of the ICD to Visit 4. Concomitant and prior vaccines and concomitant medications will be coded using the WHO Drug Dictionary.

### 3.5. Safety Endpoints

Local reactions, systemic events, AEs, SAEs, and NDCMCs have been described above (Section 3.1.1) in the primary safety endpoints.

## 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 pneumococcal immunogenicity | All randomized participants who<br>• receive the assigned investigational products at Visit 1 for the (SIIV+20vPnC)/saline group or receive the assigned investigational products at both Visit 1 and Visit 2 for the (SIIV+saline)/20vPnC group<br>• have the blood collection within 27 to 49 days after 20vPnC (Visit 2 for the [SIIV+20vPnC]/saline group, Visit 3 for the [SIIV+saline]/20vPnC group)<br>• have at least 1 valid OPA result from the blood sample collected 1 month after vaccination with 20vPnC<br>• have no other major protocol deviations as determined by the clinician |
| Evaluable HAI immunogenicity | All randomized participants who<br>• receive the assigned investigational products at Visit 1<br>• have the Visit 2 blood collection within 27 to 49 days after vaccination with SIIV<br>• have at least 1 valid HAI titer for any of the HAI strains in SIIV at Visit 2 |

| Population | Description |
|---|---|
| | • have no other major protocol deviations as determined by the clinician |
| [redacted] | CCI [redacted] |
| Safety | All randomized participants who receive 1 dose of 20vPnC or SIIV or saline and have safety follow-up after any dose. |

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations, ie, the evaluable pneumococcal immunogenicity population for OPA titers and the evaluable HAI immunogenicity population for HAI titers.

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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.

## 5. GENERAL METHODOLOGY AND CONVENTIONS

### 5.1. Hypotheses and Decision Rules

Hypothesis testing will be used to assess the 2 primary immunogenicity objectives.

#### 5.1.1. Pneumococcal Immunogenicity Hypotheses

The null hypothesis ($H_{01}$) for each pneumococcal serotype is

$$H_{01}: \ln(\mu_A) - \ln(\mu_B) \leq \ln(0.5)$$

where ln(0.5) corresponds to a 2-fold margin for the assessment of NI with respect to the immune responses to 20vPnC and

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

NI for serotype-specific OPA titers for each serotype will be formally evaluated by a 2-sided 95% CI for the ratio of serotype-specific OPA GMTs ([SIIV+20vPnC]/saline group over [SIIV+saline]/20vPnC group) 1 month after vaccination with 20vPnC. The null hypothesis ($H_{01}$) will be rejected and NI for a serotype will be declared if the lower bound of the 2-sided 95% CI for the GMR of the (SIIV+20vPnC)/saline group to the (SIIV+saline)/20vPnC group is greater than 0.5 (2-fold criterion) for that serotype.

### 5.1.2. SIIV Immunogenicity Hypotheses

The null hypothesis ($H_{02}$) for each SIIV strain-specific antibody is

$$H_{02}: \ln(\mu_C) - \ln(\mu_D) \leq \ln(0.67)$$

where ln(0.67) corresponds to a 1.5-fold margin for assessment of NI with respect to the immune responses to SIIV and

- $\ln(\mu_C)$ is the natural log of the SIIV strain-specific HAI GMT 1 month after coadministration of SIIV and 20vPnC for the (SIIV+20vPnC)/saline group
- $\ln(\mu_D)$ is the natural log of the SIIV strain-specific HAI GMT 1 month after SIIV administration for the (SIIV+saline)/20vPnC group

NI for strain-specific HAI titers will be formally evaluated by a 2-sided 95% CI for the ratio of strain-specific HAI GMTs ([SIIV+20vPnC]/saline group over [SIIV+saline]/20vPnC group) 1 month after SIIV. The null hypothesis ($H_{02}$) will be rejected and NI for strain-specific HAI will be declared if the lower bound of the 2-sided 95% CI for the GMR of the coadministration group to the separate-administration group is greater than 0.67 (1.5-fold criterion).

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## 5.2. General Methods

Time points for local reactions and systemic events refer to data within 10 days and 7 days, respectively, after each vaccination.

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 Data

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 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[2] method.

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.

Between-group comparisons will be calculated for Tier 2 AEs specified as following:

- After vaccination with SIIV and 20vPnC for the (SIIV+20vPnC)/saline group vs after vaccination with SIIV and saline for the (SIIV+saline)/20vPnC group

- After vaccination with SIIV and 20vPnC for the (SIIV+20vPnC)/saline group vs after vaccination with 20vPnC for the (SIIV+saline)/20vPnC group

Between-group comparisons will be calculated for local reactions and systemic events specified as following:

- After vaccination with SIIV and 20vPnC for the (SIIV+20vPnC)/saline group vs after vaccination with 20vPnC for the (SIIV+saline)/20vPnC group

### 5.2.2. Analyses for Continuous Data

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 and strain-specific HAI titers will be analyzed on the natural log scale, and the results will be reported on the original scale after exponentiation.

#### 5.2.2.1. Geometric Mean Titers

For immunogenicity results of serotype-specific OPA titers and the strain-specific HAI 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

Model-Based GMR

As the primary approach to calculate the GMR and CI for each serotype of OPA titer 1 month after 20vPnC, a linear regression model that includes terms for prior pneumococcal vaccine status, age at vaccination at Visit 1, corresponding baseline OPA titer, sex, smoking status, and vaccine group will be used to calculate the serotype-specific OPA GMR and the associated 95% CI, along with the model-based LS GMTs and associated 2-sided 95% CIs for each vaccine group.

As the primary approach to calculate the GMR and CI for each strain of HAI titer 1 month after SIIV, a linear regression model that includes terms for prior pneumococcal vaccine status, age at vaccination at Visit 1, corresponding baseline HAI titer, sex, smoking status, and vaccine group will be used to calculate the strain-specific HAI GMR and the associated 95% CI, along with the model-based LS GMTs and associated 2-sided 95% CIs for each vaccine group.

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#### 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.

# 6. ANALYSES AND SUMMARIES

## 6.1. Primary Endpoints

### 6.1.1. Primary Safety Endpoints

#### 6.1.1.1. Prompted Local Reactions

Prompted local reactions after each vaccination of 20vPnC or saline at Visit 1 and Visit 2 will be summarized separately.

##### 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 vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 10 days after each vaccination.
- Analysis methodology: Descriptive statistics. The between-group difference and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method (Section 5.2.1).
- Intercurrent events and missing data: Missing values will not be imputed. CCI [redacted]
- 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 after vaccination in each vaccine group will be presented by maximum severity level. Between-group differences (see Section 5.2.1) in these percentages and their 2-sided 95% CIs will also be provided.

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[redacted]

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[redacted]

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#### 6.1.1.2. Prompted Systemic Events

Prompted systemic events after each vaccination (vaccination at Visit 1 and vaccination at Visit 2) will be summarized separately.

##### 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 vaccination (Section 2.1).

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

CCI [redacted]


[redacted]

CCI [redacted]

#### 6.1.1.3. Adverse Events

AEs after each vaccination (vaccination at Visit 1 and vaccination at Visit 2) will be summarized separately.

##### 6.1.1.3.1. Main Analysis

- Estimands:
  - The percentages of participants reporting AEs within 1 month after vaccination at Visit 1 (Section 2.1).
  - The percentages of participants reporting AEs within 1 month after vaccination at Visit 2 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 1 month after each 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, 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 between-group difference and 95% CIs will be calculated for 1 month after SIIV and 20vPnC for the (SIIV+20vPnC)/saline group vs 1 month after SIIV and saline for the (SIIV+saline)/20vPnC group, and for 1 month after SIIV and 20vPnC for the (SIIV+20vPnC)/saline group vs 1 month after 20vPnC for the (SIIV+saline)/20vPnC group.

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

If any nonserious AEs are reported to occur before vaccination at Visit 1 or between 1 month after the last vaccination received in the group and the 6-month follow-up (between Visit 3 and Visit 4) (outside of the protocol-specified reporting window), they will not be summarized but will be included in the AE listings.

CCI [redacted]

#### 6.1.1.4. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

##### 6.1.1.4.1. Main Analyses

- Estimands:
  - The percentage of participants reporting SAEs up to 6 months after the last vaccination (Section 2.1).
  - The percentage of participants reporting NDCMCs up to 6 months after the last vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Up to 6 months after the last vaccination.
- Analysis methodology: Descriptive statistics.
- Intercurrent events and missing data: No missing values will be imputed except for partial SAE/NDCMC 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 2-sided 95% Clopper-Pearson CI for participants reporting any SAEs/NDCMCs, each system organ class, and each preferred term within system organ class will be presented by vaccine group. SAEs and NDCMCs will be presented separately. There will be a listing of all AEs, including SAEs and NDCMCs, and a separate listing of SAEs only.

### 6.1.2. Primary Immunogenicity Endpoints

#### 6.1.2.1. Pneumococcal Serotype-Specific OPA Titers 1 Month After Vaccination With 20vPnC

##### 6.1.2.1.1. Main Analysis

- Estimand: GMR of the serotype-specific OPA titers 1 month after vaccination with 20vPnC from the coadministration group to the serotype-specific OPA titers 1 month after vaccination with 20vPnC from the separate-administration group (Section 2.1).

- Analysis set: Evaluable pneumococcal immunogenicity population, CCI [redacted]

- Analysis time point: 1 Month after vaccination with 20vPnC. One month after vaccination with 20vPnC refers to 1 month after vaccination with 20vPnC and SIIV (Visit 2) for the (SIIV+20vPnC)/saline group and 1 month after vaccination with 20vPnC (Visit 3) for the (SIIV+saline)/20vPnC group.

- Analysis methodology: Linear regression model that includes terms for prior pneumococcal vaccine status, age (at vaccination at Visit 1), corresponding baseline OPA titer, sex, smoking status (current smoker, ex-smoker, never smoked), and vaccine group (Section 5.2.2.2). NI for a serotype will be declared if the lower bound of the 2-sided 95% CI for the GMR of the (SIIV+20vPnC)/saline group to the (SIIV+saline)/20vPnC group is greater than 0.5 (2-fold criterion) for that serotype.

- Intercurrent events and missing data: Missing serology results will not be imputed. Titers below LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis.

- 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 each of the 20 pneumococcal serotypes.

**Figures:**

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

CCI [redacted]

### 6.1.2.2. Strain-Specific HAI Titers 1 Month After Vaccination With SIIV

#### 6.1.2.2.1. Main Analysis

- Estimand: GMR of the strain-specific HAI titers 1 month after vaccination with SIIV from the coadministration group to the corresponding strain from the separate-administration group (Section 2.1).
- Analysis set: Evaluable HAI immunogenicity population, CCI [redacted]
- Analysis time point: 1 Month after vaccination with SIIV. One month after vaccination refers to 1 month after vaccination with SIIV (Visit 2) for both vaccine groups.
- Analysis methodology: Linear regression model that includes terms for prior pneumococcal vaccine status, age (at vaccination at Visit 1), corresponding baseline HAI titer, sex, smoking status (current smoker, ex-smoker, never smoked), and vaccine group (Section 5.2.2.2). NI for strain-specific HAI will be declared if the lower bound of the 2-sided 95% CI for the GMR of the coadministration group to the separate-administration group is greater than 0.67 (1.5-fold criterion).
- Intercurrent events and missing data: Missing serology results will not be imputed. Titers below LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis.
- Reporting results: The LS GMTs and associated 95% CIs for strain-specific HAI titers from each vaccine group, as well as the model-based HAI GMRs with their associated 95% CIs, will be summarized separately for each strain of HAI titer.

**Figures:**

A forest plot of GMRs with 95% CIs for all strains, with a vertical reference line corresponding to a GMR of 0.67, will be presented.

CCI [redacted]

### 6.2. Secondary Endpoints

#### 6.2.1. Secondary Pneumococcal Immunogenicity Endpoints

##### 6.2.1.1. Fold Rises in Pneumococcal Serotype-Specific OPA Titers 1 Month After Vaccination With 20vPnC

- Estimand:
  - GMFR in serotype-specific OPA titers from before to 1 month after 20vPnC.
- Analysis set: Evaluable pneumococcal immunogenicity population, CCI [redacted]
- Analysis time point: 1 Month after vaccination with 20vPnC.
- Analysis methodology: Descriptive statistics (Section 5.2.2.3).
- Reporting results: For each of the 20 vaccine serotypes, the number of participants (n), GMTs at before and 1 month after vaccination, GMFRs from before vaccination to 1 month after vaccination, and the corresponding 2-sided 95% CIs for serotype-specific OPA titers will be presented for each vaccine group.

#### 6.2.1.2. Participants With a ≥4-Fold Rise in Serotype-Specific OPA Titers From Before to 1 Month After 20vPnC

- Estimand:
  - The percentage of participants with a ≥4-fold rise in serotype-specific OPA titers from before vaccination to 1 month after vaccination.
- Analysis set: Evaluable pneumococcal immunogenicity population, CCI [redacted]
- Analysis time point: 1 Month after vaccination with 20vPnC.
- Analysis methodology: Descriptive statistics (Section 5.2.2.3).
- Reporting results: The proportion of participants with a ≥4-fold rise from before vaccination to 1 month after vaccination and associated 95% CI for the 20 matching serotypes will be summarized by vaccine 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 as well.

### 6.2.2. Secondary SIIV Immunogenicity Endpoint

#### 6.2.2.1. Fold Rises in SIIV Strain-Specific HAI Titers 1 Month After Vaccination With SIIV

- Estimand:
  - GMFR in strain-specific HAI titers from before vaccination to 1 month after vaccination.
- Analysis set: Evaluable HAI immunogenicity population, CCI [redacted]
- Analysis time point: 1 Month after vaccination with SIIV.
- Analysis methodology: Descriptive statistics (Section 5.2.2.3).
- Reporting results: For each of the strains, the number of participants (n), GMTs at before and 1 month after vaccination, GMFRs from before vaccination to 1 month after vaccination, and the corresponding 2-sided 95% CIs for strain-specific HAI titers will be presented for each vaccine group.

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[redacted]

[redacted]

[redacted]

### 6.5. Baseline and Other Summaries and Analyses

#### 6.5.1. Baseline Summaries

##### 6.5.1.1. Demographic Characteristics

Demographic characteristics, including age, sex, race, ethnicity, and prior pneumococcal vaccine status, will be summarized by vaccine group for all participants in the safety population and evaluable immunogenicity populations. Descriptive statistics (n and %) will be provided for overall and subgroup tables.

CCI [redacted]

##### 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.

CCI [redacted]

### 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 group and the vaccines actually received will be presented for each vaccine group.

### 6.5.4. Nonstudy Vaccinations and Concomitant Medications Used to Treat SAEs and NDCMCs

Each nonstudy vaccine will be summarized according to the ATC fourth-level classification. The number and percentage of randomized participants receiving each nonstudy vaccine will be listed.

Concomitant medications used to treat SAEs and NDCMCs will be summarized by vaccine group for the safety population.

### 6.6. Safety Summaries and Analyses

Summaries and analyses of the safety measures local reactions, systemic events, AEs, SAEs, and NDCMCs are described under Primary Safety Endpoints (Section 6.1.1).

## 7. INTERIM ANALYSES

### 7.1. Introduction

Not applicable.

CCI

## 8. REFERENCES

1. Collett D. Statistical inference for binary data. 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 |
| ATC | Anatomic Therapeutic Chemical |
| 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 |
| HAI | hemagglutination inhibition assay |
| ICD | informed consent document |
| IWR | interactive Web-based response |
| LLOQ | lower limit of quantitation |
| LS | least squares |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N/A | not applicable |
| NDCMC | newly diagnosed chronic medical condition |
| NI | noninferiority |
| OPA | opsonophagocytic activity |
| PPSV23 | 23-valent pneumococcal polysaccharide vaccine |
| CCI | [redacted] |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SIIV | seasonal inactivated influenza vaccine |
| WHO | World Health Organization |