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SYNOPSIS

Study Title: Final Report: A Phase 3, Randomized, Double-Blind, Third-Party Unblind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Japanese Infants

Study Number: B7471016

Regulatory Agency or Public Disclosure Identifier Number: 2022-001146-38

Study Phase: 3

Name of Study Intervention: 20-valent Pneumococcal Conjugate Vaccine (20vPnC), Compound Number: PF-06482077

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Final CSR Version 1.0, 05 October 2022

Number of Study Center(s) and Investigator(s):

A total of 668 participants were enrolled at 38 centers in Japan.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Not applicable.

Study Period:

Study Initiation Date: 16 September 2020

Primary Completion Date: 02 April 2022

This study was neither discontinued nor interrupted.

Rationale:

In Japan, 7-valent pneumococcal conjugate vaccine (7vPnC) and 13-valent pneumococcal conjugate vaccine (13vPnC) have been administered to infants by subcutaneous (SC) injection on a 4-dose vaccination schedule (3 doses for infant series and 1 dose for toddler dose). [redacted]

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The purpose of this study was to provide key safety and comparative immunogenicity data in Japanese infants to support licensure in this population in Japan. The targeted age of the population for this study, infants ≥2 to ≤6 months of age, has been selected as the routinely recommended vaccination schedule for pneumococcal conjugate vaccines and other vaccines in infants starts at approximately 2 months of age. The participants were administered either 20vPnC (SC or IM injection) or 13vPnC SC by the same injection route for all 4 doses.

Objectives, Endpoints, and Statistical Methods:

Study objectives, estimands, and endpoints are provided in Table S1.

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Table S1. Study Objectives, Estimands, and Endpoints

Primary Safety Objective	Estimands	Primary Safety Endpoints
• To describe the safety profile of 20vPnC by both SC injection and IM injection	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination: • The percentage of participants reporting prompted local reactions at injection site of investigational product within 7 days after each vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after each vaccination in each group • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 3 in each group • The percentage of participants reporting AEs from Dose 4 to 1 month after Dose 4 in each group • The percentage of participants reporting SAEs up to 1 month after Dose 4 in each group • The percentage of participants reporting NDCMCs up to 1 month after Dose 4 in each group	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs

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Table S1. Study Objectives, Estimands, and Endpoints

Primary Immunogenicity Objectives	Estimands	Primary Immunogenicity Endpoints
For 20vPnC SC group:		
• To demonstrate the percentage of participants with predefined serotype-specific IgG concentrations for the 13 serotypes in the 20vPnC SC group are noninferior to the percentage of the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	In participants in compliance with the key protocol criteria (evaluable participants) at 1 month after Dose 3: • For each of the 13 matched serotypes: difference in the percentage of participants with predefined serotype-specific IgG concentrations between the 20vPnC SC group and the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate the percentage of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest percentage among the 13 serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations, between the 20vPnC SC group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentration
For 20vPnC IM group:		
• To describe the immune responses to 20 serotypes induced by 20vPnC given by IM injection at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations between the 20vPnC IM group and the 20vPnC SC group	• Pneumococcal serotype-specific IgG concentration

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Table S1. Study Objectives, Estimands, and Endpoints

Secondary Immunogenicity Objectives	Estimands	Secondary Immunogenicity Endpoints
• To demonstrate the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC SC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of serotype-specific IgG concentrations from the 20vPnC SC group to the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
• To demonstrate the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest IgG GMC among the 13 serotypes induced by the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in • 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC SC group to the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
• To further describe the immunogenicity of 20vPnC by both SC and IM injection	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: GMR of serotype-specific IgG concentrations from the 20vPnC IM group to the 20vPnC SC group In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: Serotype-specific IgG GMCs at 1 month after Dose 4 in each group In evaluable participants at 1 month after Dose 3 and 1 month after Dose 4: • Serotype-specific OPA GMTs at 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4 in each group In evaluable participants at 1 month after Dose 4:	• Pneumococcal serotype-specific IgG concentrations • Pneumococcal serotype-specific IgG concentrations • Pneumococcal serotype-specific OPA titers • Pneumococcal serotype-specific IgG concentrations

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Table S1. Study Objectives, Estimands, and Endpoints

	• For each of the serotypes in 20vPnC: percentage of participants with the predefined serotype-specific IgG concentration in each group	
	In evaluable participants: • GMFRs in serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 in each group	• Pneumococcal serotype-specific IgG concentrations
Exploratory Immunogenicity Objectives	**Estimands**	**Exploratory Immunogenicity Endpoints**
[redacted]		

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Table S1. Study Objectives, Estimands, and Endpoints

Abbreviations: 13vPnC =13-valent pneumococcal conjugate vaccine; 20vPnC = 20-valent pneumococcal conjugate vaccine; AE = adverse event; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMR = geometric mean ratio; IgG = immunoglobulin G; IM = intramuscular; [redacted]; NDCMC = newly diagnosed chronic medical condition; OPA = opsonophagocytic activity; SAE = serious adverse event; SC = subcutaneous.

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Methodology:

This Phase 3, multicenter, randomized, double-blinded, third party unblinded study was conducted at investigator sites in Japan. [redacted] The purpose of this study was to describe safety and conduct the pivotal immunogenicity comparison of 20vPnC administered by SC injection to the licensed pneumococcal conjugate vaccine, 13vPnC, administered by the currently indicated SC injection [redacted] in Japan. Data was generated from 20vPnC administered by IM injection, with the 20vPnC administered by SC as a control.

This study planned to enroll approximately 666 infants between 2 through 6 months of age at the time of consent by their parent(s)/legal guardian(s). Participants were randomized equally to 1 of the following vaccine groups: (1) 20vPnC SC group, (2) 13vPnC SC group (control vaccine), or (3) 20vPnC IM group. Participants received the same vaccine (20vPnC or 13vPnC) by the same injection method (SC or IM injection) for all 4 doses at Visits 1, 2, 3, and 5 (refer to the protocol Schedule of Activities table for the timing of the visits; Figure S1). All vaccine groups were blinded to all members of the site involved in the study except unblinded staff who administered 20vPnC or 13vPnC.

Local reactions (redness, swelling, and pain at the injection site), systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), and use of antipyretic/pain medication were prompted for and collected by the participant's parent(s)/legal guardian(s) in an e-diary, via device or application, from Day 1 through Day 7 after each vaccination (where Day 1 is the day of vaccination).

Adverse events (AEs)were collected from the time the participant's parent(s)/legal guardian(s) provided informed consent through 1 month after Dose 3 (Visit 4) and from Dose 4 (Visit 5) through 1 month after Dose 4 (Visit 6). SAEs and NDCMCs were collected from informed consent through 1 month after Dose 4 (Visit 6).

Blood was collected 1 month after Dose 3 (Visit 4), immediately prior to Dose 4 (Visit 5), and 1 month after Dose 4 (Visit 6) to assess immunogenicity.

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Figure S1. Study Design Overview

Number of Participants (Planned and Analyzed):

Approximately 666 participants were planned to be enrolled. A total of 668 participants were randomized, 659 (98.7%) participants completed the Dose 3 follow-up visit, and 649 (97.2%) completed all visits per protocol.

A total of 667 participants were included in the safety population. One (1) participant randomized to the 20vPnC IM was excluded from the safety population due to not receiving any study treatment.

A total of 659 (98.7%) participants were included in the all-available immunogenicity population, with the primary reason for exclusion being no valid immunogenicity results. The primary reason for exclusion from the Dose 3 or Dose 4 evaluable immunogenicity populations was not receiving the assigned vaccine, as randomized, for first 3 or all 4 doses, respectively. Of those vaccinated, 654 (97.9%) participants received all 3 infant doses and 648 (97.0%) participants received all 4 doses.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Participants included healthy Japanese male or female infants ≥2 months to ≤6 months (defined as the first day the participant is 2 months of age to the last day the participant is 6 months of age) at the time of consent.

Participants were excluded from the study if they had a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the investigational product, the specified concomitant vaccines, or any diphtheria toxoid-containing vaccine. Additional exclusion criteria included any contraindication to vaccination with pneumococcal conjugate vaccine or the specified concomitant vaccines, significant neurological disorder or history of seizure, major known congenital malformation or serious chronic disorders, history of microbiologically proven invasive disease caused by *Streptococcus pneumoniae*, known or suspected immunodeficiency or other conditions associated with immunosuppression, congenital, functional, or surgical asplenia, and other

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acute or chronic medical or psychiatric condition or laboratory abnormality that might increase the risk associated with study participation. Participants were excluded from the study if they had a history of previous vaccination with any licensed or investigational pneumococcal vaccine, prior receipt of *Haemophilus influenzae* type b, Hepatitis B (Hep B), rotavirus, diphtheria, tetanus, acellular pertussis, and/or poliovirus vaccines, currently receiving treatment with immunosuppressive therapy, or receipt of blood/plasma products or immunoglobulins (including Hep B immunoglobulin and monoclonal antibodies) since birth or planned receipt through the last planned blood sample collection in the study (through Visit 6).

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Participants received 1 dose of 20vPnC or 13vPnC at each vaccination visit (Visits 1, 2, 3, and 5 with Doses 1, 2, 3, and 4, respectively). Doses 1 to 3 were preferred to be administered at 2, 3, and 4 months of age consistent with the vaccination schedule recommended by the Japan Pediatric Society. In addition, Dose 3 was to be completed by 12 months of age and Dose 4 was to be administered ≥60 days after Dose 3.

In the 20vPnC SC and 13vPnC SC groups, 20vPnC or 13vPnC was administered subcutaneously by injecting 0.5 mL into the anterolateral thigh (preferably into the left anterolateral thigh) at the vaccination visits. In the 20vPnC IM group, 20vPnC was administered intramuscularly by injecting 0.5 mL into the anterolateral thigh muscle of the leg (preferably of the left leg) at the vaccination visits.

The manufacturing lot numbers for the study intervention(s) dispensed in this study are provided in Table S2.

Table S2. Investigational Product Lot Numbers

Investigational Product	Manufacturer	Vendor Lot Number (Manufacturer)	Lot Number[a] (Pfizer)
20vPnC	Pfizer	DW1636	20-002030
13vPnC	Pfizer	DN3806	20-001731

a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply.
Protocol B7471016 Investigational Product Lot Numbers Table – Final, Version 1.0, 05Aug2022.

Duration of Study Intervention:

Each participant participated in the study for approximately 7 to 14 months depending on the age of enrollment in the study.

Summary of Results:

Demographic and Other Baseline Characteristics:

Demographic and baseline characteristics of sex, race, ethnicity, and age for the safety population were balanced across the vaccine groups. Across the vaccine groups, all

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participants were Asian (Japanese), 49.4% were males, and median age at first dose was 2.3 months.

Exposure:

Of the 668 participants enrolled in the study, 659 participants (98.7%) were vaccinated through Dose 3 and 651 (97.5%) participants received Dose 4.

Immunogenicity Results:

Response to 20vPnC compared to 13vPnC

The percentage of participants with predefined serotype-specific IgG concentrations 1 month after Dose 3 of 20vPnC SC was noninferior to 13vPnC SC for 11 of the 13 matched serotypes (all but serotypes 6A and 6B), and to the lowest serotype in the 13vPnC SC group for 5 of 7 additional serotypes (all but serotypes 10A and 12F). Out of the 13 matched serotypes, 6A and 6B missed this endpoint by a small margin. The totality of data supports that the immune responses elicited by 20vPnC are expected to be effective against disease caused by the 20 vaccine serotypes, including those that missed NI.

- Post hoc analysis with alternative defined level of ≥0.15 μg/mL for IgG concentrations at this time point showed that serotype 6A would have met NI of 20vPnC SC to 13vPnC SC at this level with the same NI criterion.

- The majority of participants (90.0% for serotype 6A and 87.8% for serotype 6B) in the 20vPnC SC group had predefined IgG concentrations for those serotypes 1 month after Dose 3, with increases at 1 month after Dose 4 of 20vPnC SC (100% for serotypes 6A and 6B) comparable to 13vPnC SC.

- The majority of participants (60.2% for serotype 10A and 74.7% for serotype 12F) in the 20vPnC SC group had predefined IgG concentrations at this time point with increases at 1 month after Dose 4 of 20vPnC SC (>98.4% for all of the 7 additional serotypes).

- The IgG GMCs 1 month after Dose 3 of 20vPnC SC were noninferior to 13vPnC SC for 10 of the 13 matched serotypes and to 6 of the 7 additional serotypes compared to the lowest in the 13vPnC SC group. Serotypes 5, 6A, 6B, and 10A missed NI; serotypes 5, 6A, and 10A missed the statistical criterion by a small margin.

- [redacted]
  - [redacted]

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[redacted]

- Following 3 infant doses of 20vPnC SC, infants were primed for memory responses to the 13 matched vaccine serotypes, similar to the 13vPnC SC. This was shown by IgG GMFRs from 1 month after Dose 3 to 1 month after Dose 4 >1.0 for all serotypes except serotype 3. The IgG GMFRs in the 20vPnC SC group for the serotypes that missed NI for the primary objective (serotypes 6A, 6B, 10A, and 12F) were 3.4 or higher 1 month after Dose 4. Boosting from before Dose 4 to 1 month after Dose 4 was also observed for all serotypes. [redacted]

- Observed IgG and OPA responses for all 7 additional serotypes were much higher in the 20vPnC SC group (consistent with superior, statistically significantly higher antibody levels) when compared with the corresponding serotype responses in the 13vPnC SC group. Therefore, 20vPnC elicits potentially protective antibody responses in infants that are not available in existing vaccines.

[redacted]

Safety Results:

- The percentages of participants with prompted local reactions and systemic events were generally similar in the 20vPnC SC and 13vPnC SC groups after each dose. The proportion of reported swelling and redness in the 20vPnC IM group was lower than in the 20vPnC SC and 13vPnC SC groups. Injection site redness was the most frequent local reaction reported in all groups. Most local reactions and systemic events were mild or moderate in severity.

- Rates of AEs within 1 month after Dose 3 or from Dose 4 to 1 month after Dose 4 of 20vPnC SC, 13vPnC SC, or 20vPnC IM were similar across vaccine groups. No safety concerns were identified.

- The percentages of participants with NDCMCs after Dose 1 were low (≤10.7%) and similar across the 20vPnC SC, 13vPnC SC, and 20vPnC IM groups.

- The proportion of participants with reported SAEs was low (≤7.4%) and similar across the 20vPnC SC, 13vPnC SC, and 20vPnC IM groups. Most SAEs reported were consistent with medical events that may occur in this population. One death occurred in

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the 20vPnC IM group; this event and all reported SAEs were not considered related to study intervention.

Conclusions

20vPnC SC was observed to have a similar tolerability and safety profile to 13vPnC SC. The 4-dose series of 20vPnC SC elicits immune responses that are expected to help expand protection against pneumococcal disease due to the 7 additional serotypes, while maintaining existing protection currently controlled by 13vPnC in Japanese infants.

[redacted] The 2 modes of administration were observed to have a similar safety and tolerability profile with the exception of injection site swelling and redness, which were lower when 20vPnC was administered IM.