

CLINICAL STUDY REPORT SYNOPSIS

Vaccine Name and Compound Number: 13-valent Pneumococcal Conjugate Vaccine (diphtheria CRM197 protein), Compound Number: PF-05208760

Report Title: Final Report: A Phase 3, Multicenter, Single-Arm, Open-Label Study to Assess the Safety, Tolerability, and Immunogenicity of a Single Dose of 13-Valent Pneumococcal Conjugate Vaccine in Japanese Subjects Aged 6 to 64 Years Who are Considered to be at Increased Risk of Pneumococcal Disease and Who are Naive to Pneumococcal Vaccines

Protocol Number: Protocol B1851172

Sponsor: Pfizer, Inc.

Phase of Development: Phase 3

First Subject First Visit: 12 July 2018

Last Subject Last Visit: 16 November 2018

Serology Completion Date:

IgG: 16 March 2019

OPA: 23 May 2019

Coordinating/Lead Investigator:

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Study Center(s):

This study was undertaken at 8 sites in Japan.

Date of Current Version: 17 July 2019

Date of Previous Report: Not applicable.

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OBJECTIVES

Primary and Secondary Study Objectives and Endpoints:

Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
Safety	<ul style="list-style-type: none"> To assess the safety and tolerability of a single dose of 13vPnC as measured by the incidence of local reactions, systemic events, AEs, and SAEs. 	<ul style="list-style-type: none"> Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 7-day period following study vaccination in the 6- to <18-year age group. Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 14-day period following study vaccination in the 18- to <65-year age group. Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 7-day period following study vaccination in the 6- to <18-year age group. Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 14-day period following study vaccination in the 18- to <65-year age group. Number and proportion of subjects reporting AEs and SAEs until Visit 2 categorized according to the MedDRA in all age groups.
Secondary		
Immunogenicity	<ul style="list-style-type: none"> To describe the immune responses elicited by a single dose of 13vPnC. 	<ul style="list-style-type: none"> Serotype-specific OPA GMTs 1 month after vaccination in all age groups. GMFRs in serotype-specific OPA titers from before vaccination to 1 month after vaccination in all age groups. Serotype-specific IgG GMCs 1 month after vaccination in all age groups. GMFRs in serotype-specific IgG from before vaccination to 1 month after vaccination in all age groups.
Abbreviations: GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; IgG = immunoglobulin G; OPA = opsonophagocytic activity.		

METHODS

Study Design:

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This was a Phase 3, multicenter, single-arm, open-label study to assess the safety, tolerability, and immunogenicity of a single dose of 13-valent pneumococcal conjugate vaccine (13vPnC) in Japanese subjects aged 6 to 64 years who were considered to be at increased risk of pneumococcal disease (PD) and who were naïve to pneumococcal vaccines.

This study consisted of 2 age groups: 6 to <18 and 18 to <65 years old. Approximately 200 subjects were to be enrolled: approximately 50 subjects in the 6- to <18-year age group and approximately 150 subjects in the 18- to <65-year age group. For the purpose of ensuring a minimum number of subjects in each of the age categories, at least 15 subjects aged 6 to <12 years and 15 subjects aged 12 to <18 years were to be enrolled within the 6- to <18-year age group. Furthermore, at least 50 subjects aged 18 to <50 years and 50 subjects aged 50 to <65 years were to be enrolled within the 18- to <65-year age group. Subjects participated in the study for approximately 1 month (29 to 43 days).

Inclusion/Exclusion Criteria:

Inclusion Criteria

Subjects had to meet all of the following inclusion criteria to be eligible for enrollment into the study:

- Evidence of a personally signed and dated informed consent document indicating that the subject and/or a legally acceptable representative/parent/legal guardian for subjects considered to be minors in Japan (6 to <20 years old) was informed of all pertinent aspects of the study.
- Japanese males and females aged 6 to <65 years at enrollment.
- Availability for the entire duration of the study, and subjects (and a legally acceptable representative/parent/legal guardian if the subject was 6 to <18 years old) who were willing and able to comply with scheduled visits, vaccination plan, and other study procedures including completion of the e-diary for 7 days (Day 1 to Day 7) for subjects aged 6 to <18 years or 14 days (Day 1 to Day 14) for subjects aged 18 to <65 years after study vaccination.
- Subjects with an increased risk of PD determined by documented medical history, physical examination, and clinical judgment of the investigator. The risks may have included but were not limited to stable chronic heart disease, lung disease, liver disease, or renal disease; diabetes mellitus (DM); hematologic or solid organ malignancy; immunocompromised persons with known or suspected immunodeficiency due to underlying diseases or treatments; subjects with anatomic host defense abnormalities such as cochlear implants or cerebral spinal fluid leaks.
- Subject (and/or a legally acceptable representative/parent/legal guardian if the subject was 6 to <18 years old) was able to be contacted by telephone during study participation.

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- Male subjects able to father children and female subjects of childbearing potential who were, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) agreed to use a highly effective method of contraception throughout the study and for at least 28 days after vaccination.

Female subjects of non-childbearing potential who met at least 1 of the following criteria:

1. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone level confirming the postmenopausal state.
2. Had undergone a documented hysterectomy and/or bilateral oophorectomy.
3. Had medically confirmed ovarian failure.
4. Female subjects who were <9 years old. If the female subject who was <9 years old had experienced menarche at an earlier age, the subject was considered of childbearing potential.

All other female subjects (including female subjects with tubal ligations) were considered to be of childbearing potential.

Exclusion Criteria

Subjects with any of the following characteristics/conditions were not included in the study:

- Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt during study participation.
- Unstable chronic medical condition or disease requiring significant change¹ in therapy or hospitalization for worsening disease within 6 weeks before investigational product (IP) administration.
- End-stage disease including but not limited to metastatic² malignancy, severe chronic obstructive pulmonary disease requiring supplemental oxygen, or end-stage renal disease with or without dialysis.

¹ Change in dose or therapy within a category (eg, change from 1 nonsteroidal anti-inflammatory drug [NSAID] to another) was allowed. Change to new therapy categories (eg, surgery, or addition of a new pharmacological class) was allowed only if it was not caused by worsening disease. If change to new therapy categories was caused by worsening disease, this was considered significant.

² Subjects with lymph node and/or distant metastases.

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- Graft-versus-host disease, history of solid organ transplant within 6 months before IP administration or history of hematopoietic stem cell transplant (HSCT), or potential for solid organ transplant or HSCT during study participation.
- Receipt of cytotoxic chemotherapy or blood products within 3 months before IP administration or anti-B-cell antibodies within 6 months before IP administration through completion of study participation.
- Any contraindication to vaccination or vaccine components, including previous anaphylactic reaction to any vaccine or vaccine-related components.
- Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate any type of injection.
- Vaccination with a diphtheria-containing vaccine or toxoid within 6 months before IP administration through the completion of the study participation.
- Documented *S pneumoniae* infection within the past 5 years before IP administration.
- Insufficient muscle mass, in the opinion of the investigator, to receive a vaccination in the deltoid muscle of the arm.
- Residence in a nursing home or long-term care facility, or requirement for semiskilled nursing care. An ambulatory subject who was a resident of a retirement home or village was eligible for the trial.
- Severe visual impairment requiring third-party support to read.
- Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
- Participation in other studies involving investigational drug(s) or vaccine(s) within 28 days prior to study entry and/or during study participation. Participation in purely observational studies was acceptable.
- Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or IP administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
- Pregnant female subjects as determined by urine pregnancy test (human chorionic gonadotropin); breastfeeding females; fertile male and female subjects of childbearing

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potential who were unwilling or unable to use a highly effective method of contraception for the duration of the study and for at least 28 days after vaccination.

Vaccines Administered:

All subjects received a single dose (0.5 mL) of 13vPnC intramuscularly at Visit 1 (Day 1). Per 0.5-mL dose, the vaccine was formulated to contain 4.4 µg of saccharide from pneumococcal serotype 6B and 2.2 µg of each of the other 12 saccharides (1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

Immunogenicity Evaluations:

In total, 2 blood samples were collected at Day 1 (Visit 1) prior to receipt of IP and 1 month later (28 to 42 days after Visit 1) (Visit 2) for assessment of the immune responses. A quantitative functional opsonophagocytic activity (OPA) assay and Luminex-based antibody-binding assay were used to measure antibody-mediated serum OPA and serum concentrations of anticapsular immunoglobulin G (IgG) antibodies for each of the 13 pneumococcal serotypes, respectively.

Safety Evaluations:

Starting on the day of vaccination, local reactions (redness, swelling, and pain at the injection site), systemic events (fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain), axillary temperature, and the use of antipyretic medication and pain medication for treatment of symptoms were recorded in the e-diary for 7 days by the subject's legally acceptable representative/parent/legal guardian for subjects aged 6 to <18 years or 14 days by the subject for subjects aged 18 to <65 years. Fever was defined as an axillary temperature of $\geq 37.5^{\circ}\text{C}$ and analyzed as a systemic event.

Adverse events (AEs), including serious AEs (SAEs) were recorded on the AE page(s) of the case report form (CRF) from the time the subject/legally acceptable representative/parent/legal guardian provided informed consent through and including Visit 2. Reactions within the first 30 minutes after IP administration were assessed and documented in the AE CRF as immediate AEs.

The grading scales used in this study to assess local reactions and systemic events were derived from the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical studies. If required on the AE page of the CRF, the investigator used the adjectives mild, moderate, severe, or life-threatening to describe the maximum intensity of the AE.

Statistical Methods:

General Methods

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Descriptive summaries included the following statistics: number and percent of subjects, mean, standard deviation, median, minimum, maximum, and the 2-sided 95% confidence interval (CI).

Other estimations are presented below.

Geometric Mean: For each serotype, OPA geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs) were calculated.

Geometric Mean Fold Rise: For each serotype, OPA and IgG geometric mean fold rises (GMFRs) were calculated.

Reverse Cumulative Distribution Curve: For each serotype, the empirical reverse cumulative distribution curves (RCDCs) plotted the percentage of subjects achieving a given titer or concentration.

Methods to Manage Missing Data and Data Below the Lower Limit of Quantitation

For the analysis of the immunogenicity endpoints, missing values were retained as missing and were not imputed.

For OPA titers and IgG concentrations, values below the lower limit of quantitation (LLOQ) were set to $0.5 \times \text{LLOQ}$ for analysis.

Analysis Populations

The analysis populations are presented below.

Safety Analysis Set

The safety population included all subjects who received 1 dose of study vaccine. The safety population was the only analysis population for the primary endpoints.

Evaluable Immunogenicity Population

The evaluable immunogenicity population was the primary immunogenicity analysis population. It included subjects who met the following:

1. Were eligible for the study based on the inclusion and exclusion criteria.
2. Received the study vaccine
3. Received no prohibited vaccines.

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4. Had blood drawn within the specified time frame 1 month after vaccination (28 to 42 days after Visit 1 [ie, Day 29 to Day 43 when Day 1 was vaccination visit]).
5. Had at least 1 valid and determinate assay result (OPA titer or IgG concentration) for at least 1 serotype 1 month after vaccination.
6. Had no major protocol violations as determined by the sponsor's clinician, or any other protocol deviations that would materially affect assessment of immunogenicity endpoints.

All-Available Immunogenicity Population

The all-available immunogenicity population included all subjects who were enrolled, received the study vaccine, and had at least 1 valid and determinate assay result (OPA titer or IgG concentration) for at least 1 serotype 1 month after vaccination.

RESULTS

Subject Disposition and Demography: All 206 screened subjects (200 planned for enrollment) were enrolled and completed the study.

No enrolled subjects were excluded from the all-available immunogenicity population or the evaluable immunogenicity population and therefore the all-available and evaluable immunogenicity populations were identical.

Overall, 51.9% of subjects were male and 48.1% of subjects were female; all subjects were Japanese. The mean ages at vaccination were 12.7 years (range: 7 to 17 years) in the 6- to <18-year age group and 49.0 years (range: 20 to 64 years) in the 18- to <65-year age group. Considering individuals who smoke are considered to be at increased risk for developing PD, it is worth noting that 22.2% and 22.9% of subjects aged ≥ 18 years were current or former smokers, respectively, at the time of enrollment.

Demographic characteristics for the all-available immunogenicity and evaluable immunogenicity populations were the same as for the safety population.

Among subjects aged 6 to <18 years, the most common chronic medical conditions that put these subjects at increased risk of PD (and cited in $\geq 5\%$ of subjects) were grouped under the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) of: cardiac disorders; congenital, familial and genetic disorders³; hepatobiliary disorders; neoplasms benign, malignant and unspecified; renal and urinary disorders; respiratory, thoracic and mediastinal disorders. The most common preferred terms (PTs) that

³ PTs within the SOC category of congenital, familial and genetic disorders that investigators considered increased the risk of PD were benign familial pemphigus, heterotaxia, hypertrophic cardiomyopathy, hypoplastic left heart syndrome, primary ciliary dyskinesia, primary immunodeficiency syndrome, renal hypoplasia, and univentricular heart.

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investigators considered increased the risk of PD were: asthma, type 1 DM, nephrotic syndrome, type 2 DM, non-alcoholic fatty liver, and acute lymphocytic leukemia. In addition, 15.1% of subjects were treated with immunosuppressive therapy during the study, which was also considered a factor that increased risk of PD in these subjects.

Among subjects aged 18 to <65 years, the most common chronic medical conditions that put these subjects at increased risk of PD (and cited in $\geq 5\%$ of subjects) were grouped under the MedDRA SOCs of: cardiac disorders; hepatobiliary disorders; neoplasms benign, malignant and unspecified; renal and urinary disorders; respiratory, thoracic and mediastinal disorders. The most common PTs that investigators considered increased the risk of PD were: type 2 DM, rheumatoid arthritis, non-alcoholic fatty liver, asthma and atypical mycobacterial lower respiratory tract infection. In addition, 24.8% of subjects were treated with immunosuppressive therapy during the study, which was also considered a factor that increased risk of PD in these subjects.

Immunogenicity Results:

- For subjects aged 6 to <65 years, OPA GMTs for each of the 13 pneumococcal serotypes were higher 1 month after vaccination compared to before vaccination. The OPA GMFRs observed from baseline to 1 month after vaccination ranged from 5.5 to 61.7 and the lower limits of the 2-sided, 95% CIs for the OPA GMFRs were >1 for each of the 13 serotypes, indicating that subjects had an immune response to the vaccine. OPA GMT increases and OPA GMFRs were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.
- The majority of subjects (range: 78.9% to 95.0%) aged 6 to <65 years achieved an OPA titer \geq LLOQ 1 month after vaccination for each of the 13 pneumococcal serotypes. The proportions of subjects who achieved an OPA titer \geq LLOQ were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.
- The majority of subjects (range: 56.4% to 80.9%) aged 6 to <65 years achieved a ≥ 4 -fold increase in OPA titer for each of the 13 pneumococcal serotypes. The proportions of subjects who achieved a ≥ 4 -fold increase in OPA titer were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.
- For subjects aged 6 to <65 years, RCDCs for each of the 13 pneumococcal serotypes showed higher proportions of subjects that achieved a given OPA titer 1 month after vaccination compared to before vaccination. The proportions of subjects achieving the specified pneumococcal OPA titer for each of the 13 serotypes 1 month after vaccination were generally higher across the full range of antibody titers in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.
- For subjects aged 6 to <65 years, IgG GMCs for each of the 13 pneumococcal serotypes were low before vaccination and higher 1 month after vaccination. The IgG GMFRs

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observed from baseline to 1 month after vaccination ranged from 4.605 to 47.565 and the lower limits of the 2-sided, 95% CIs for the IgG GMFRs were >1 for each of the 13 serotypes, indicating that subjects had an immune response to the vaccine. IgG GMC increases and IgG GMFRs were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.

- The majority of subjects (range: 73.3% to 89.3%) aged 6 to <65 years achieved a ≥ 4 -fold increase in IgG concentration for each of the pneumococcal vaccine serotypes except for serotype 3 (49.0% of subjects). The proportions of subjects who achieved a ≥ 4 -fold increase in IgG concentration were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.
- For subjects aged 6 to <65 years, RCDCs for each of the 13 pneumococcal serotypes showed higher proportions of subjects achieved a given IgG concentration 1 month after vaccination compared to before vaccination. The proportions of subjects achieving the specified pneumococcal IgG concentrations for each of the 13 serotypes 1 month after vaccination were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.
- Overall, a single administration of 13vPnC in Japanese subjects aged 6 to <65 years who were considered to be at increased risk of PD (and who were naïve to pneumococcal vaccines) elicited robust immune responses 1 month after vaccination.

Safety Results:

- The majority of subjects reported any local reactions within 7 days after vaccination in the 6- to <18-year age group (82.7%) and 14 days after vaccination in the 18- to <65-year age group (67.1%). In both age groups, pain at the injection site was the most frequently reported local reaction. The majority of local reactions were mild or moderate in severity, except for 1 case of severe swelling in the 6- to <18-year age group and 2 cases of severe pain at the injection site in the 18- to <65-year age group. The proportions of subjects who reported local reactions were generally higher in the 6- to <18-year age group than in the 18- to <65-year age group.
- The majority of subjects reported any systemic events within 7 days after vaccination in the 6- to <18-year age group (60.8%) and 14 days after vaccination in the 18- to <65-year age group (58.6%). In both age groups, the 3 most frequently reported systemic events were fatigue, muscle pain, and headache. The majority of systemic events were mild or moderate in severity, except for 1 case each of severe fatigue and severe headache in the 6- to <18-year age group, and 1 case each of severe diarrhea, severe muscle pain, and severe joint pain in the 18- to <65-year age group. The proportions of subjects who reported systemic events were broadly similar in the 6- to <18-year and 18- to <65-year age groups.

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- Overall, few AEs were reported (16.0% of subjects overall). There were no SAEs, life-threatening AEs, or immediate AEs reported during the study. There were no deaths, and no subjects were withdrawn for safety-related reasons during the study.
- AEs that were assessed by the investigator to be related to IP were reported by 6 (2.9%) subjects. These were mild events associated with IP injection site reaction, except for 1 event each of decreased appetite and middle insomnia.
- Two (2) subjects reported severe AEs, including 1 AE of severe back pain and 1 AE of severe asthma, neither of which was assessed as vaccine related.
- Overall, 13vPnC was well tolerated with an acceptable safety profile in Japanese subjects aged 6 to <65 years who were considered at increased risk of PD and naïve to pneumococcal vaccines.

Conclusions:

In Japanese individuals aged 6 to <65 years who were considered to be at increased risk of PD and who were naïve to pneumococcal vaccines, 13vPnC was immunogenic for each of the 13 serotypes and was well-tolerated with an acceptable safety profile. The results support the extension of the indication of 13vPnC for the prevention of PD in Japan.