

Application Type	Original BLA
STN	125731/0
CBER Received Date	October 8, 2020
PDUFA Goal Date	June 8, 2021
Division / Office	DVRPA/OVRR
Committee Chair	Christina Houck
Clinical Reviewer(s)	Tina Mongeau
Project Manager	Juan Lacayo, Diana Oram, Kamal Velmurugan
Priority Review	Yes
Reviewer Name(s)	Ruoxuan Xiang
Review Completion Date / Stamped Date	
Concurrence	Lihan Yan Team Lead, Vaccine Evaluation Branch (VEB), Division of Biostatistics (DB), Office of Biostatistics and Epidemiology (OBE)
	Tsai-Lien Lin Branch Chief, VEB/DB/OBE
	John Scott Director, DB/OBE
Applicant	Pfizer Inc.
Established Name	20-valent Pneumococcal Conjugate Vaccine
(Proposed) Trade Name	Prevnar20
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	2.2 µg of each of 20 saccharides, except for 4.4 µg of 6B, (b) (4) succinate buffer, (b) (4) sodium chloride, (b) (4) polysorbate 80, and 0.125 mg aluminum as aluminum phosphate
Dosage Form(s) and Route(s) of Administration	0.5 mL suspension for intramuscular injection, supplied in a single-dose pre-filled syringe
Dosing Regimen	single dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of pneumonia and invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older

Table of Contents

1. Executive Summary	3
2. Clinical and Regulatory Background	3
3. Sources of Clinical Data and Other Information Considered in the Review	4
3.1 Review Strategy	4
3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review	4
4. Discussion of Individual Studies/Clinical Trials	4
5. Conclusions	9

1. Executive Summary

Pfizer, the applicant, submitted the original Biologics License Application (BLA) STN 125731/0 for the 20-valent Pneumococcal Conjugate Vaccine (20vPnC) as a rolling submission, completed on October 8, 2020. The vaccine is indicated for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F in adults 18 years of age and older.

20vPnC is a sterile liquid suspension for intramuscular injection, developed to expand protection against the global burden of vaccine-preventable disease caused by *Streptococcus pneumoniae* over that of currently marketed Prevnar 13 (13vPnC). 20vPnC contains the same 13 serotype-specific capsular polysaccharide antigens included in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), plus 7 additional serotype-specific capsular polysaccharides (8, 10A, 11A, 12F, 15B, 22F, and 33F). The 7 additional serotypes not covered by 13vPnC are included in the currently marketed unconjugated polysaccharide vaccine, Pneumovax 23 (PPSV23; Merck Sharp & Dohme Corp).

It was agreed that an indication for invasive pneumococcal disease (IPD) would be supported for the 7 additional serotypes if the immunological success criteria for these serotypes were met (with a totality of data approach), as it would establish a bridge between 20vPnC and PPSV23, which has been shown to be effective against IPD. However, PPSV23 has not been demonstrated to be effective in the prevention of nonbacteremic pneumococcal pneumonia. The FDA agreed that immunogenicity data for the 7 additional serotypes may be used as the basis for supporting the accelerated approval for a pneumonia indication in adults for these serotypes. A well-designed real-world observational effectiveness study with pre-specified endpoints measuring protection against pneumonia caused by the 7 additional serotypes would be required to confirm the clinical benefit as a confirmatory study after licensure.

This memo documents the review of the proposed post-marketing requirement (PMR) study of the effectiveness of 20vPnC against pneumonia caused by the 7 additional serotypes. The study protocol synopsis was submitted to IND 17039. Several information requests (IRs) regarding the protocol were communicated to the applicant during the IND and BLA stages. To date, discussion of the protocol for the confirmatory study is still ongoing. One outstanding issue is related to whether the primary analysis population is to be restricted to the five-year PPSV23-naïve population. Agreement on the final protocol is expected to be reached post-licensure within an agreed time frame. Nevertheless, the current version of the protocol appears to be generally acceptable and does not preclude the approval of this application.

2. Clinical and Regulatory Background

On November 8, 2019, FDA agreed in principle that an indication for the prevention of pneumonia caused by the 7 additional serotypes could be supported by immune responses as measured by OPA assay under an accelerated approval pathway. Continued approval

for this indication would be contingent upon verification and description of clinical benefit in a confirmatory post authorization commitment, real-world observational effectiveness study. In addition, the review team sent some IR comments regarding the proposed Phase 4 observational study submitted to IND 17039.58.

On April 30, 2020, the applicant submitted the response to FDA November 8, 2019 IR to IND 17039.104.

On July 20, 2020, the review team sent a further IR comment regarding the sample size calculation for the observational study.

On January 15, 2021, the applicant submitted the revised protocol and the response to the July 20, 2020 IR to BLA 125731/0.8.

On March 19, 2021, the applicant submitted the response to FDA March 12, 2021 IR to BLA 125731/0.25.

On May 5, 2021, the applicant submitted to the response to FDA April 28, 2021 IR to BLA 125731/0.33.

3. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

3.1 Review Strategy

The statistical review of the clinical and non-clinical data submitted to this BLA are documented in the respective memos. This memo focuses on the review of the PMR study proposal.

3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents were reviewed:

- 125731/0.8 Module 1.17.2 Correspondence Regarding Postmarketing Requirements
- 125731/0.25 Module 1.11.3 Clinical Information Amendment
- 125731/0.33 Module 1.11.3 Clinical Information Amendment

4. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The PMR study B7471015 is entitled “A phase 4 study using a test-negative design to evaluate the effectiveness of a 20-valent pneumococcal conjugate vaccine against vaccine-type radiologically confirmed community-acquired pneumonia in adults \geq 65 years of age.” The primary objective is to determine the effectiveness of 20vPnC against all (invasive + non-invasive) radiologically confirmed community-acquired pneumonia (RAD+CAP) due to the 7 additional serotypes plus cross-reacting serotype 15C.

In the test-negative design (TND), participants are enrolled based on a clinical case definition (i.e., RAD+CAP). Participants are then tested for the 7 additional serotypes

plus 15C, and the vaccine effectiveness (VE) is estimated from the odds ratio (OR) comparing the odds of vaccination among participants testing positive for the 7 additional serotypes plus 15C vs. those testing negative, adjusting for potential confounding factors. Case in the TND for the primary efficacy analysis is defined as 7 additional serotypes in 20vPnC beyond 13vPnC plus 15C identified by any method and the test-negative control is defined as non-20vPnC serotypes, identified by any method, plus all other RAD+CAP of non-pneumococcal etiology. Table 1 below lists the definition of case and test-negative control for the primary and secondary VE objectives. Please refer to the clinical reviewer's memo for the review of the case and control definitions.

Table 1. Definitions of Cases, and Test-negative Controls for Primary and Secondary Objectives

	Objectives	CAP definition	Case	Control
Primary	To determine the effectiveness of 20vPnC against all (invasive + non-invasive) RAD+CAP due to the 7 additional serotypes in 20vPnC beyond 13vPnC plus 15C.	RAD+CAP	7 additional serotypes in 20vPnC beyond 13vPnC plus 15C identified by any method	Non-20vPnC serotypes, identified by any method, plus all other RAD+CAP of non-pneumococcal etiology
Secondary 1	To determine the effectiveness of 20vPnC against non-invasive RAD+CAP due to the 7 additional serotypes in 20vPnC beyond 13vPnC plus 15C (i.e., restricted to participants where <i>S. pneumoniae</i> is not isolated from a normally sterile site.	Non-invasive RAD+CAP	7 additional serotypes in 20vPnC beyond 13vPnC plus 15C not identified from a normally sterile site specimen	Non-20vPnC serotypes, not identified from a normally sterile site specimen, plus all other RAD+CAP of non-pneumococcal etiology
Secondary 2	To determine the effectiveness of 20vPnC against all RAD+CAP due to any 20vPnC serotype plus 6C and 15C.	RAD+CAP	20vPnC serotypes plus 6C and 15C identified by any method	Non-20vPnC serotypes, identified by any method, plus all other RAD+CAP of non-pneumococcal etiology
Secondary 3	To determine the effectiveness of 20vPnC against non-invasive RAD+CAP due to any 20vPnC serotype plus 6C and 15C.	Non-invasive RAD+CAP	20vPnC serotypes plus 6C and 15C not identified from a normally sterile site specimen	Non-20vPnC serotypes, not identified from a normally sterile site specimen, plus all other RAD+CAP of non-pneumococcal etiology

Source: Adapted from Table 1 in the protocol submitted to BLA 125731/0.8.

TND is less susceptible to bias caused by differences in healthcare-seeking behavior among cases and controls. In general, healthcare-seeking behavior will be an unmeasured

confounder in traditional cohort or case-control studies that could threaten the validity of VE estimates. By conditioning on participants presenting to healthcare providers with the same clinical syndrome, the TND helps reduce bias due to (unmeasured) healthcare seeking behavior.

Statistical Hypothesis

H₀: OR > δ, where δ = 0.8, i.e., VE for the primary objective < 20% vs.

H₁: OR ≤ δ, i.e., VE ≥ 20%

Sample size determination

The sample size calculation is based on the normal approximation of the log form of the odds ratio. The required number of controls is

$$n_C = \frac{(z_\alpha + z_\beta)^2}{(\log(OR) - \delta)^2} \left(\frac{1}{kp_T(1-p_T)} + \frac{1}{p_C(1-p_C)} \right),$$

where α = 0.025, β = 0.1, and z_α, z_β are the upper α and upper β quantiles, respectively. p_T and p_C are the proportions of subjects who are vaccinated with 20vPnC among cases and controls, respectively.

Reviewer's Comment:

In the sample size determination section of the protocol, the applicant provided a literature reference in which the formula for n_C was derived from a prospective parallel design, and p_T and p_C were defined as the probabilities of observing an outcome of interest for a patient treated by the vaccine or a placebo (the control), respectively. Following the same argument as in the literature, one can obtain the same formula above for n_C in a case-control design, with p_T and p_C defined as the proportions of subjects who are vaccinated with 20vPnC among cases and controls, respectively.

The total sample size is

$$N = n_C (k + 1),$$

Where k is the ratio of cases and controls.

The assumptions used to estimate the sample size of the analysis population for evaluation of vaccine effectiveness are:

1. 1:31 ratio of cases to controls (3% of participants will be defined as a case, and 93% of participants will be defined as a control)
2. 20% of participants will have received 20vPnC (based on the assumption that ACIP will recommend 20vPnC for routine use among 13vPnC naïve adults ≥65 years of age)
3. 70% true VE
4. 1-sided test with significance level α=0.025
5. 90% power

In addition to these assumptions, there are 3 factors that impact the total number of enrolled participants:

1. The proportion of participants with complete vaccination history available: estimated to be 70%

2. The proportion of participants with CAP and adjudicated radiology reading: estimated to be 65%
3. The proportion of participants excluded due to being positive for 13vPnC serotypes: estimated to be 4%

Based on the assumptions above, 170 cases are needed in the primary VE analysis with 5285 controls according to the expected case-control ratio. After applying the adjustment factor to estimate the total number of participants that need to be enrolled such that the primary analysis sample size will be achieved, a total of approximately 12500 participants will need to be enrolled in the study to identify the required 170 cases.

Reviewer's Comment:

Previously in the sample size calculation submitted to IND 17039.104, the applicant assumed a true VE of 45%, 20% controls exposed to 20vPnC, and ratio of controls to cases = 8, then the resulting lower bound of the 95% CI for VE would be equal to 20% if the number of cases is 273. This calculation did not consider that the assumed rates are subject to variability, therefore, the sample size did not reflect the intended 90% power for testing the null hypothesis of VE=20%. In the IR sent on July 20, 2020, we requested the applicant to revise the sample size calculation. In the IR response submitted to BLA 125731/0.8, the applicant revised the calculation and described the statistical approach used in the sample size calculation, which is described above. The applicant also provided the rationale for revising some of the assumptions. For example, the true assumed VE was updated to 70% from 45% and the ratio of controls to cases was updated to 31:1 from 8:1. I defer the acceptability of the assumed VE and the rationale to the clinical and epidemiological reviewers.

Efficacy analysis

The primary analysis population is RAD+CAP population which include all participants who:

1. Meet all inclusion and exclusion criteria,
2. Have radiologic imaging confirmed to be consistent with pneumonia by adjudication process,
3. Have 5 years of documented pneumococcal vaccination history ascertained from participant's primary care physician records, the participant's electronic medical record, pharmacy records, insurance claims data, or state registries,
4. Did not receive a pneumococcal vaccine ≤ 30 days prior to enrollment,
5. Did not receive the (b) (4) which is under development by (b) (4) or an investigational pneumococcal vaccine.

Vaccine exposure for the primary analysis will be receipt of 20vPnC > 30 days prior to hospital admission for CAP. Vaccine effectiveness will be estimated using generalized estimating equation with logit link function that includes pre-specified prognostic covariates, including exposure of 20vPnC, age, risk group (i.e., the presence of an ACIP-defined at-risk or high-risk condition), influenza vaccination status, and season.

Reviewer's Comments:

1. *In the protocol submitted to BLA 125731/0.8, the applicant proposed to select the variables that were independently associated with the outcome at $p < 0.10$ in a bivariate analysis and include those variables in the multivariable model to adjust for potential confounding variables. This variable selection strategy might be more susceptible to selecting non-confounders or excluding important confounders (e.g., influenza vaccination) and therefore introducing bias. Due to the ambiguity in the variable selection process, we suggest that the applicant pre-specify a set of prognostic covariates that are anticipated to be strongly associated with the outcome in the statistical model as the primary efficacy analysis. Inclusion of additional covariates in the model may be considered in the sensitivity analyses. In the response submitted to BLA 125731/0.25, the applicant agreed to our recommendation and stated that the covariates including exposure of 20vPnC, age, risk group (i.e., the presence of an ACIP-defined at-risk or high-risk condition), influenza vaccination status, and season, will be collected and included in the multivariable model to estimate adjusted vaccine effectiveness for the primary analysis. I consider this response acceptable.*
2. *Although it was not formally defined in the primary analysis population, participants vaccinated with PPSV23 prior to 20vPnC will be excluded from the analysis. However, subjects vaccinated with PPSV23 after 20vPnC will be included in the primary analysis population. Since PPSV23 is expected to provide protection against invasive pneumococcal pneumonia caused by the 7 additional serotypes, inclusion of subjects vaccinated with PPSV23 may confound the evaluation of the effectiveness of 20vPnC. In the IR sent on April 28, 2021, we recommended that the applicant use the five-year PPSV23-naïve population, which is a subset of the RAD+CAP population that includes participants who have not received PPSV23 within the last 5 years, as the primary analysis population for the primary endpoint and key secondary endpoint. We also advised that other approaches to account for the impact of PPSV23 exposure five years prior to hospitalization may be used as secondary analysis. In the response submitted to BLA 125731/0.33, the applicant argued against excluding participants who received PPSV23 after 20vPnC from the primary analysis population with two reasons: 1. It is the recommended schedule per ACIP guidelines. If the recommendation is adhered to rigorously, the percent of participants who have received PCV20 only (without subsequent PPSV23) could be small and result in a study that is impractical to accomplish; 2. PPSV23 is not considered to have impact on non-bacteremic pneumonia as recognized by the US CDC or ACIP, and the proportion of all CAP due to the 7 additional serotypes in PCV20 beyond PCV13 due to bacteremic CAP is expected to be small. Consequently, the potential incremental impact of PPSV23 on prevention of bacteremic CAP due to these serotypes would be negligible and too small to affect interpretation of vaccine effectiveness estimates in a meaningful way. Nevertheless, the applicant proposed to adjust VE estimates for the receipt of PPSV23 after 20vPnC in the multivariable regression model. This issue remains outstanding at this time and will be resolved with the applicant post-licensure.*

5. CONCLUSIONS

The general design of the confirmatory study is acceptable. Discussion of the protocol for the confirmatory study is still ongoing. The applicant did not agree to change the primary analysis population to the five-year PPSV23-naïve population, which was recommended by the review team. This issue remains outstanding at this time and will be resolved with the applicant post-licensure. Nevertheless, the current version of the protocol does not preclude licensure of this product.