NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	IMmunization to Prevent Acute COPD Exacerbations (IMPACE STUDY)
Protocol number	PFI-INM-2016-01 (B1851177)
Protocol version identifier	Version 2
Date of last version of protocol	31 October 2016
Active substance	Pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 Protein)
Medicinal product	Prevnar13
Research question and objectives	To evaluate the impact of vaccination with PCV13 on the reduction of the risk of moderate/severe exacerbations (see definitions), after 2 years of follow up and to determine which subgroup of patients benefit most from vaccination with PCV13
Author	Redacted [redacted]

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
COPD	Chronic Obstructive Pulmonary Disease
AECOPD	Acute Exacerbation of COPD
CAP	Community acquired pneumonia
P-CAP	Pneumococcal Community Acquired Pneumonia
PCV13	13 valent pneumococcal conjugate vaccine
PPV23	23 valent pneumococcal polysaccharide vaccine
FSFV	First subject first visit
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
CRF	Case Report Form
EDP	Exposure During Pregnancy
HCP	Healthcare practitioner
IEC	Independent Ethic Committee
IRB	Institutional Review Board
LSLV	Last Subject Last Visit
NIS	Non-Interventional Study
SAE	Serious Adverse Event
AE	Adverse Event
AEM	Adverse Event Monitoring

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
[redacted]	Redacted	[redacted]	[redacted]

Country Coordinating Investigators

Name, degree(s)	Title	Affiliation	Address
[redacted]	[redacted]	Redacted	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

3. ABSTRACT

SPONSOR:

Redacted

Contact person:

Redacted

STUDY TITLE

IMmunization to Prevent Acute COPD Exacerbations (IMPACE STUDY)

PROTOCOL CODE: B1851177

COORDINATING INVESTIGATOR(S):

The scientific coordinators shall be responsible for maintaining the methodological rigour of the study, both in the design period and in the assessment of the results and preparation of the final report. They shall ensure the study is conducted ethically, maintaining the scientific support for all physicians participating until the publication of the study results:

Redacted

STUDY SITES:

It has been initially estimated as optimum that patient inclusion be performed in 6 different geographical areas in Spain (Salamanca, Cantabria, Palma de Mallorca, Madrid, Barcelona and Seville), involving 1 hospital in each region.

IEC EVALUATING IT

- This protocol will be submitted for approval to a reference IEC (Hospital Clínico de Salamanca) and for classification to the Ministry of Health according to Spanish regulation.
- It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, if

applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

- The study will not start until every needed approval of the study protocol and other essential documents will be obtained.
- The study investigator, or a study person designated by the investigator, will obtain written informed consent from each subject or the patient´s legally acceptable representative before any study-specific activity is performed.

STUDY OBJECTIVES

- **Primary objectives**

1. Evaluate the impact of routine clinical practice vaccination with PCV13 on the reduction of the risk of moderate/severe COPD exacerbations (see definitions) in adults, after 2 years of follow up.
2. Determine which subgroup of patients (based on the severity of COPD) benefit most from vaccination with PCV13

   COPD severity (GOLD)[18]
   - GRADE 1: Mild/unknown [FEV1≤ 80%, FEV1/FVC < 0,7 or no spirometry data]
   - GRADE 2: Moderate [50% ≤ FEV1< 80%,FEV1/FVC < 0,7]
   - GRADE 3: Severe [30% ≤ FEV1 < 50%, FEV1/FVC < 0,7]
   - GRADE 4: Very severe [FEV1< 30% o FEV1< 50% plus respiratory failure,FEV1/FVC < 0,7])

- **Secondary objectives**

1. Evaluate the impact of influenza and PCV13 vaccination on the reduction of the risk of exacerbations
2. Evaluate the impact of vaccination with PCV13 on patients' quality of life
3. Evaluate the impact of vaccination with PCV13 on the decrease of FEV1
4. Estimate the potential economic savings for the healthcare system derived from vaccination of COPD patients with PCV13
5. Determine the prevalence of PCV13 vaccination in COPD patients.

DESIGN

Prospective multicenter observational study, carried out in 6 different geographical areas in Spain (Salamanca, Cantabria, Palma de Mallorca, Madrid, Barcelona and Seville), involving 1 hospital in each region.

STUDY DISEASE

Patients with chronic obstructive pulmonary disease (COPD) have been demonstrated to have an increased risk of pneumococcal disease. Pneumonia is frequent among patients hospitalized for COPD exacerbations and is associated with increased health care utilization and higher mortality. Up to 50%–70% of exacerbations can be attributed to respiratory infections by viruses or bacteria, even more in the most severe patients. They are often associated with the colonization of airways by multiple bacteria or viruses of low virulence that in normal conditions are parts of the normal flora of the upper airway. Current recommendations for immunization of patients with COPD include vaccination against influenza and *Streptococcus pneumoniae*.

The aim of this study is to generate evidence to support vaccination of COPD patients with PCV13 and/or against influenza in terms of clinical benefits and also quality of life.

STUDY POPULATION AND TOTAL NO. OF SUBJECTS

Periodic follow up of COPD patients is usually performed at ambulatory setting (may be at hospital or primary care centers). Commonly, databases containing clinical information for a patient are accessible from both settings, so data from previous years would be available to compare with data captured prospectively to the same standards.

Subjects identified with COPD will be informed about the study and invited to participate by investigators at the time of their routine control visits. All therapies will be prescribed according to the updated National COPD Guidelines (GesEPOC)[1] indicating among other therapies active reduction of risk factors, influenza and pneumococcal vaccination (with PCV13) in all patients with mild, moderate or severe COPD. All the patients will be counselled to stop smoking and advised on life-style modifications. Any vaccination will be prescribed according to clinical practice and not related to the decision to include the subjects in the study. Subjects may be vaccinated before or after inclusion in the study.

Considering that 37% of COPD patients would have a moderate/severe exacerbation per year,[2] and assuming that at least 35% of patients will follow their pulmonologist vaccination recommendation,[3] to have at least 200 vaccinated COPD patients with moderate/severe exacerbations, a total sample of 1541 eligible COPD patients should be included in the analysis.

CALENDAR

- Protocol submission to IEC and to the Ministry of Health is expected to be done by September 2016 in order to obtain approvals in November 2016.
- Financial agreements with the sites are expected to be obtained from December 2016 to February 2017.
- Recruitment of participant subjects is expected to start (FSFV) in January 2017. The recruitment will end in January 2019.
- Database is expected to be completed and closed by April 2019. Data analysis is expected by September 2019. Study results are expected by October 2019.

FUNDING SOURCE

This study is sponsored by Pfizer

4. AMENDMENTS AND UPDATES

None

5. MILESTONES

Milestone	Planned date
Completion of site selection	1 July 2016
Start of data collection (FSFV)	8 January 2017
End of data collection (LSLV)	31 January 2019
Study results	1 September 2019
Final study report	31 October 2019

6. RATIONALE AND BACKGROUND

Patients with chronic obstructive pulmonary disease (COPD) have been demonstrated to have an increased risk of pneumococcal disease.[4,5] Pneumonia is frequent among patients hospitalized for COPD exacerbations and is associated with increased health care utilization and higher mortality. Nonpneumonic COPD exacerbations predict increased risk of subsequent exacerbations.[6] Among community acquired pneumonia (CAP) patients with the highest severity of disease who require hospitalization, COPD is the most common comorbidity. These two diagnoses, CAP and acute exacerbations of COPD (AECOPD), come together when COPD patients acquire AECOPD caused by CAP.[7]

Exacerbations are a significant component of the clinical course in COPD. Furthermore, as COPD progresses, exacerbations become more frequent.[8] COPD exacerbations are defined as a complex of two or more respiratory symptoms (worsening dyspnea, cough, sputum production, chest tightness, or wheezing) related to the underlying COPD, with duration of 3 days or more, that require a change in treatment.[9] Acute exacerbations of COPD (AECOPD) have a great impact on health status,[10] disease progression,[6] and prognosis.[11] Up to 50%–70% of AECOPD can be attributed to respiratory infections by viruses or bacteria, even more in the most severe patients.[12] They are often associated with the colonization of airways by multiple bacteria or viruses of low virulence that in normal conditions are parts of the normal flora of the upper airway.[13]

Some studies have identified factors independently associated with bacterial growth, such as current smoking and *H. influenzae*; longer periods between exacerbations and *S. pneumoniae*; or decrease in FEV1 and *P. aeruginosa*.[14] Traditionally, bacterial identification has been defined depending on the severity of the COPD, since *S. pneumoniae* and *M. catharralis*, are isolated in patients with predicted FEV1 >50%, and *H. influenzae,* Enterobacteriaceae and *P. aeruginosa* in those with FEV1 <50.[14,15]

Therefore, considering *S. pneumoniae* appears to be more frequent in patients with mild/moderate COPD, these subjects might be the most benefited from a preventive approach targeting this pathogen.

In terms of costs, COPD represents a significant burden on the healthcare system. Different studies relate the costs to the severity or stage of the disease.[16] The clinical course of COPD with multiple exacerbations has generated many economic studies analyzing these episodes. Anderson et al. in 2002, concluded that severe exacerbations represent 10 times the cost of a moderate exacerbation and around 60 times the cost of a mild-moderate episode. Similarly, exacerbations in severe COPD are 45 times more costly than in mild stages of the disease. The largest proportion of the cost of exacerbations is associated with hospitalizations, representing 65-85% of the total expense per acute episode.[17]

All this evidence supports the current recommendations for immunization of patients with COPD with vaccines against influenza and *Streptococcus pneumoniae*, aimed to help prevent infectious exacerbations.[18,19] Existing studies suggest an additive effect in the prevention of all-cause mortality with influenza and pneumococcal vaccines given together in elderly people, including in those with underlying chronic disease. Although no significant reduction in mortality rate was seen with the pneumococcal vaccine (PPV23) alone, there was a decrease in mortality rate of 27.0% (20.0–34.0) in subjects who received both vaccines compared to 16.0% (6.0–24.0) in those who received influenza vaccine.[20] However, despite the existing recommendations these vaccines are generally under-used probably due to some persistent uncertainty about the benefits of vaccination.[21]

There are two types of pneumococcal vaccines, a 23 valent polysaccharide vaccine and a 13 valent conjugate vaccine. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is approved and recommended for use in persons ≥2 years of age for the prevention of pneumonia and pneumococcal disease.[22] In the past decades many studies have evaluated the effect of PPV23 in adults, and effectiveness in preventing IPD has been reported, but with a short duration of protection, and limited impact on the total burden of disease even in countries with high uptake.[23,24] Regarding the prevention of noninvasive pneumococcal pneumonia, the most common clinical presentation of the disease in adults, studies assessing the effectiveness of PPV23 show inconsistent results.[25] Moreover, the available studies focused specifically on COPD patients, do not show a clear effect on any of the outcomes evaluated (developing pneumonia or acute exacerbations).[26]

The 13 valent pneumococcal conjugate vaccine was approved by the EMA for the prevention of IPD in adults ≥50 in 2011, and subsequently in 2013 for adults ≥18 years of age, based on immunogenicity studies.[27] Following the publication of the results of the CAPiTA study in 2015, showing the efficacy of the vaccine for the prevention of bacteremic (45,6%) and non-baceteremic (45%) pneumococcal pneumonia, and IPD (75%) caused by PCV13 serotypes in subjects ≥65 years old, the EMA approved the indication for the prevention of pneumonia in adults aged ≥18 years.[28,29]

Recent exploratory studies have shown a beneficial effect of PCV13 in reducing the number of exacerbations in COPD and other respiratory diseases.[30,31] Results from a group of 90 COPD patients vaccinated with PCV13 and followed for 2 years in Spain, showed a reduction of 50% in the number of severe exacerbations in the second year after immunization.[32] A prospective comparative open label study carried out in Russia, evaluating PCV13 safety and effectiveness to prevent CAP in COPD patients compared with non-vaccinated patients, found in a group of 25 patients a 4.8-fold reduction in the incidence of exacerbations one year after vaccination.[31]

The limitations of these preliminary results require larger studies, specifically designed for this purpose, to assess which sub-groups might benefit most from this preventive approach.

The aim of this study is to generate evidence to support vaccination of COPD patients with PCV13 and/or against influenza in terms of clinical benefits and also quality of life.

7. RESEARCH QUESTION AND OBJECTIVES

- **Primary objectives**
  1. Evaluate the impact of routine clinical practice vaccination with PCV13 on the reduction of the risk of COPD moderate/severe exacerbations (see definitions) in adults, after 2 years of follow up.
  2. Determine which subgroup of patients (based on the severity of COPD) benefit most from vaccination with PCV13

     COPD severity (GOLD)[18]
     - GRADE 1: Mild/unknown [FEV1≤ 80%, FEV1/FVC < 0,7 or no spirometry data]
     - GRADE 2: Moderate [50% ≤ FEV1< 80%,FEV1/FVC < 0,7]
     - GRADE 3: Severe [30% ≤ FEV1 < 50%, FEV1/FVC < 0,7]
     - GRADE 4: Very severe [FEV1< 30% o FEV1< 50% plus respiratory failure,FEV1/FVC < 0,7])

- **Secondary objectives**
  1. Evaluate the impact of influenza and PCV13 vaccination on the reduction of the risk of exacerbations
  2. Evaluate the impact of vaccination with PCV13 on patients' quality of life
  3. Evaluate the impact of vaccination with PCV13 on the decrease of FEV1
  4. Estimate the potential economic savings for the healthcare system derived from vaccination of COPD patients with PCV13
  5. Determine the prevalence of PCV13 vaccination in COPD patients.

8. RESEARCH METHODS

8.1. Study design

Prospective multicenter observational study, carried out in 6 different geographical areas in Spain (Salamanca, Cantabria, Palma de Mallorca, Madrid, Barcelona and Seville), involving 1 hospital in each region.

The study would be carried out by a cohort study design: using subjects not vaccinated with PCV13 included in the study as a control group.
The specific number of patients to be included will be addressed in the analysis section depending on the recruited sample.

- Patients who do not receive PCV13 vaccination recommendation from their physicians
- Patients who, even after physician recommendation, they do not receive vaccination for different reasons
- Patients with some contraindications for vaccination with PCV13

8.2. Setting

- This prospective non interventional study will be conducted by pulmonologists at hospital level. Regarding follow up or medical records, specialists may access clinical information from the Primary Care centers database related to the hospital.
- Periodic follow up of COPD patients is usually performed at ambulatory setting (may be at hospital or primary care centers). Commonly, databases containing clinical information for a patient are accessible from both settings, so data from previous years would be available to compare with data captured prospectively to the same standards.
- Recruitment will be performed in 6 hospitals in 6 geographical areas in Spain (Salamanca, Cantabria, Palma de Mallorca, Madrid, Barcelona, Seville).

Study procedures

Subjects identified with COPD will be informed about the study and invited to participate by investigators at the time of their routine control visits. All therapies will be prescribed according to the updated National COPD Guidelines (GesEPOC)[1] indicating among other therapies active reduction of risk factors, influenza and pneumococcal vaccination (with PCV13) in all patients with mild, moderate or severe COPD. All the patients will be counselled to stop smoking and advised on life-style modifications. Any vaccination will be prescribed according to clinical practice and not related to the decision to include the subjects in the study. Subjects may be vaccinated before or after inclusion in the study.

Study will include periodic scheduled visits for all patients, to complete a total follow up of 2 years (see Table 1).

8.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patient ≥18 years diagnosed with COPD (any stage, the subgroups for the analysis would be based on COPD severity grade)

2. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
3. Ability to understand and complete the required QoL questionnaires
4. At least 2 years of clinical history available that includes records of previous moderate/severe exacerbations, influenza and pneumococcal vaccination history comorbidities and previous treatments.
5. Spirometry data* (maximum 6 months old, or if not available at enrollment, to be performed as per normal clinical practice at visit 1 +/- one month)

*Subjects with FEV1 <40 should be less than 20% of the total study population (related to the microbiological etiology dependent on severity)[14,15]

8.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Impossibility to perform prospective follow up
2. Present any immunocompromising condition
3. Present any other respiratory diseases as co-morbidity (subjects with overlap syndromes COPD-asthma will be excluded. Mixed phenotype defined as: symptoms of increased variability of airflow and incompletely reversible airflow obstruction)[33]

8.3. Variables

Variables to be recorded from previous clinical history and follow up visits (according to Table 1):

- Consent date
- Subject code
- Demographic and epidemiological data;
- Antropometric data (weight, height, body mass index (BMI), Waist Circumference)
- Smoking habit, alcohol consumption
- Spirometric data (FEV1, FVC, FEV1/FVC)
- Pharmacological treatment
- COPD severity (GOLD)[18]
    - GRADE 1: Mild/unknown [FEV1≤ 80%, FEV1/FVC < 0,7 or no spirometry data]
    - GRADE 2: Moderate [50% ≤ FEV1< 80%,FEV1/FVC < 0,7]
    - GRADE 3: Severe [30% ≤ FEV1 < 50%, FEV1/FVC < 0,7]
    - GRADE 4: Very severe [FEV1< 30% o FEV1< 50% plus respiratory failure,FEV1/FVC < 0,7])
- Number and severity of exacerbations

- Frequency of total exacerbations (moderate and severe) in the previous year and during follow-up (recorded at hospital or primary care level).
- Comorbidities
    - high blood pressure
    - dyslipidemia
    - type 2 diabetes mellitus
    - metabolic syndrome
    - heart failure
    - ischemic heart disease
    - chronic kidney disease
    - cirrhosis
- History of neoplasia (solid organ and hematologic)
- Pneumococcal vaccination
- Influenza vaccination
- QoL questionnaire (reduced SGRQ, CAT) - completed by subjects and transcribed into electronic case report form (CRF)

8.3.1 Study procedures

Visit 0: selection and recruitment

- Obtain of signed informed consent document
- Confirmation of eligibility
- Assignation of subject number. Subject number will be assigned sequentially as the participants are included in the study. The number will be composed of 6 digits, first three will be the site code and last three the subject number.

Study authorized personnel will complete the case report form (CRF) for each of the subjects included. CRF (Annex 2) will be completed by an interview of the subject or review of clinical history and results of test/activities performed (as part of routine clinical practice)

Visits 1 to 5: Follow Up

Activities to be carried out in each of the follow up visits are detailed in Table 1

TABLE 1. FOLLOW UP VISITS

Visit	0	1	2	3	4	5
Month	0	1	6	12	18	24
Verification of inclusion/exclusion criteria	X	X	X	X	X	X
Informed consent signature	X					
Demographic variables	X					
Exacerbations and smoking history	X	X	X	X	X	X
Clinical history (hospital and/or primary care)	X					
Performance or verification of recent spirometry	X			X		X
Completion of QOL test	X			X		X
Treatment and vaccination recommendations adjustment (as per normal clinical practice)	X			X		X
Telephone Follow up (if applicable)			X		X	
PCV13 vaccination record		X		X		X
Influenza vaccination record		X		X		X
Updated treatment record		X		X		X

Definitions:[9]

- COPD exacerbations are defined as a complex of two or more respiratory symptoms (worsening dyspnea, cough, sputum production, chest tightness, or wheezing) related to the underlying COPD, with duration of 3 days or more, that require a change in treatment.
  - *Treatment changes* include acute treatment with antibiotics and/or steroids, or an addition of new maintenance bronchodilator.
  - *Mild exacerbations* are those that require new prescription of bronchodilator only
  - *Moderate exacerbations* are those that require antibiotics and/or systemic corticosteroids without hospitalization,
  - *Severe exacerbations* are those that lead to hospitalization.
- The onset date of exacerbations is defined by the onset of the first recorded symptom.
- Exacerbations that occur within 7 days of onset of a prior exacerbation are counted as a single exacerbation

A subject presenting with exacerbation, will be considered as vaccinated at least 15 days after receiving immunization

- Immunosupression:
  - Lymphoma/Leukemia
  - Another neoplasm subjected to immunosuppressing treatments
  - Organ transplant with its corresponding immunosuppressing treatment
  - Leukopenia<1.000/mm; neutropenia<500/mm
  - Patients infected by Human Immunodeficiency Virus (HIV)
  - Congenital immunodoficiency
  - Diseases that requires continuous treatment with systemic corticosteroids administration for more than 14 days (prednisone at doses> 15 mg/day or other equivalent preparations), or cytotoxic agents during the previous six months.

8.4. Data sources

For this study, data source will include medical records, emergency room reports, QoL questionnaires and the electronic case report form (CRF).

8.5. Study size

With 35% patients vaccinated with PCV13, enrolling 1540 eligible COPD patients will provide approximate 540 patients in PCV13 cohort and 1000 patients in the control cohort.

Assuming 37% of the control patients experiencing moderate/severe exacerbation per year with 70% of the patients remaining in the study at year 1, this sample size will provide 91% power to detect a statistical significant reduction of 10% on COPD moderate/severe exacerbations from PCV13 after 1-year. Assuming additional 30% dropout from year 2, the study sample size will provide 91% power to detect a statistical significant reduction of 14% on COPD moderate/severe exacerbations from PCV13 after 2-year.

Time	PCV13		Control		Power	Retention Rate
	Sample Size	% exacerbation	Sample Size	% exacerbation		
Enrollment	540		1000			
1-year	378	27%	700	37%	91.43%	70% from Enrollment
2-Year	264	60%	490	74%	91%	70% from Year 1

8.6. Data management

- Study data will be collected by site staff in an electronic CRF. Details on management of data included in the electronic CRF will be included in the Data Management Plan.

- In accordance with quality control criteria on collecting information, a monitor designated by Pfizer will contact the study investigator to supervise study conduct and protocol compliance according to the Monitoring Plan. To record study monitoring, the monitor will complete the Contact Report or the Monitoring Report.
- Data management system procedures including data transfer process from raw data on the electronic CRF until a 'clean' database is obtained will be described in the Data Management Plan.

8.7. Data analysis

Depending on recruitment and data availability an interim analysis may be performed after the first year, if at least 75% of subjects included have completed one year of follow up.

- To determine the impact of PCV13 vaccination, the incidence of exacerbations will be determined 2 years after the inclusion in the study and will be compared with the incidence 2 years before the study (2 years of clinical history required including records of previous moderate/severe exacerbations, influenza and pneumococcal vaccination history comorbidities and previous treatments)
- A descriptive analysis of all variables will be performed. Qualitative variables will be analyzed by absolute and relative frequencies. Quantitative variables will be studied by the usual centralization and dispersion measures (mean, median, standard deviation, confidence intervals, minimum, maximum and interquartile range).
- For comparison of independent samples, the Pearson chi-squared test or the exact Fisher test for 2x2 tables or likelihood ratio for mXn tables, for qualitative variables, will be used. The Student's t test, one-way ANOVA or its non-parametric equivalent U-Mann-Mann, H-Kruskal-Wallis for quantitative variables will be used.
- For comparison of paired samples, the McNemar's test will be used for qualitative variables and Student's t test or Wilcoxon's test for quantitative variables.
- A multivariate logistic regression analysis will be performed, in order to identify risk factors associated with exacerbations. Exacerbations existence (yes/no) will be used as dependent variable. Vaccination with PCV13 and statistically significant variables in the univariate model, will be used as possible risk factors: demographic characteristics, influenza vaccination, smoking habit, etc. In addition, potential confounding variables will be considered: phenotype, comorbidities, COPD severity, FEV1 (no control possible based on the study design)
- Appropriate tests will be performed accordingly to determine if the necessary requirements are fulfilled for the use of parametric contrasts.
- Estimates will be performed with a 95% confidence interval. The SPSS statistical package version 19.0 or later will be used.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality control

- In accordance to quality control criteria on collecting information, a monitor designated by Pfizer will contact the study GP to supervise study conduct and compliance according to the Monitoring Plan. Monitoring of data collected in the electronic CRF may be done at the study site and by a remote review of the data recorded. During monitoring visits data included in the electronic CRF will be verified with the original source documents and any discrepancy clarified with the site staff and resolved. To record study monitoring, the monitor will complete the Contact Report or the Monitoring Report.
- Database design, data entry and validation procedures, testing and validation will be performed according to the Data Management Plan. The discrepancy database will be reviewed and Data Clarification Forms will be generated for data clarification as required.

8.9. Limitations of the research methods

- The actual proportion of subjects who would follow their healthcare practitioner (HCP) vaccination recommendation is not known, so this aspect might influence the size of the vaccinated group and therefore the global results.
- Losses to follow-up can introduce bias in the global results obtained.
- Considering the bacterial etiology depending on disease severity, a very large percentage of patients with FEV<40%, would limit the proportion of *S.pneumoniae* presence in the study population and hence the potential impact of the immunization.
- The estimated study sample, aims to determine if there is a 10% significant reduction on the risk of all cause COPD exacerbations in PCV13 vaccinated subjects. Since there is no previous evidence to guide the reduction magnitude, this may be a potential limitation considering that experience with PCV13, coming from a large clinical trial including over 84,000 subjects only found a 5% (non-significant) reduction on all cause CAP[28] and in addition, the proportion of vaccine type infection in COPD exacerbations is not established. However, recent pilot studies results showed a significant reduction on total number of exacerbations in a small group of 90 subjects 2 years post-vaccination.[30-32, 34]

8.10. Other aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the study subject.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future

information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lost to follow-up does not constitute patient withdrawal.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The IRB/IEC must review and approve the protocol and informed consent form before any subjects provide consent.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the principles of the International Conference on Harmonization (ICH) guideline on Good Clinical Practice and applicable local regulatory requirements and laws.

9.5. Interference with the prescription habits of the physician

In no case shall the researcher's decision regarding the most appropriate treatment for the patient be interfered with.

This is an observational study; therefore, the decisions on indication of treatment and inclusion in the study shall be independent and always based on normal clinical practice.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the electronic CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving exposure to a Pfizer product, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the electronic CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE (Serious adverse event)	All (regardless of whether the event is determined by the investigator to be related to any Pfizer product)	Only events determined by the investigator to be related to a Pfizer product
Non-serious AE (Non-serious adverse event)	All (regardless of whether the event is determined by the investigator to be related to any Pfizer product)	None
Scenarios **involving exposure to a Pfizer product**, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) involving exposure to a Pfizer product

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below).

Safety events must be reported to Pfizer within 24 hours of awareness of the event by the investigator as described in the table above. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For those safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the electronic CRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's informed consent, which is obtained prior to the patient's enrollment in the study, and lasts through the end of the observation period of the study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation or failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient. If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the serious AE to be related to a Pfizer product, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to a Pfizer product, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that a Pfizer product caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and she/he cannot determine whether a Pfizer product caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that a Pfizer product did not cause the event, this should be clearly documented on the electronic CRF and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Redacted

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

<u>Abnormal test findings</u>

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Serious adverse events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported:

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) a Pfizer product, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to a Pfizer product (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to a Pfizer product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with a Pfizer product, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred, must be submitted using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to a Pfizer product, in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product

by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy, in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while

in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE :

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.1. Single reference safety document

The fact sheet will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

"The SRSD should be used by the investigator for prescribing purposes and guidance."

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

All information gathered as a result of this study shall be considered confidential.

The Sponsor's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and Sponsor policies regarding publication and communication of clinical study results.

The results of the study herein shall be the exclusive property of the Sponsor. The Scientific Coordinators of the study, together with the Sponsor, will present the results by the usual scientific means in a timely manner. The Principal Investigators may report the results at an appropriate scientific meeting and/or publish them in a reputable journal with the Sponsor's written consent. A copy of the manuscript or original shall be submitted to the Sponsor sufficiently in advance so that the Sponsor is able to make such comments and suggestions as deemed fit.

The institutions and Investigators shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Thereafter, if an Investigator expects to participate in the publication of data generated from a site, the institution and Investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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13. LIST OF TABLES

Not applicable.

14. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. CASE REPORT FORM

ANNEX 3. COORDINATING INVESTIGATOR AGREEMENT

ANNEX 4. IRB/IEC APPROVAL

ANNEX 5. PATIENT'S INFORMATION SHEET AND INFORMED CONSENT

ANNEX 6. ECONOMIC REPORT