Non-Interventional Study Protocol

C4591006

General Investigation of COMIRNATY Intramuscular Injection

(Follow-up Study for Subjects [Healthcare Professionals] Who are Vaccinated at an Early post-Approval Stage)

Statistical Analysis Plan

Version: 6.0

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1. REVISION HISTORY

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
1.0 23-MAR-2021 PPD Before Enrollment	First edition
2.0 04-AUG-2021 PPD Ongoing	Section 3 • Deleted some descriptions to allow for interim analyses that will be performed for purposes other than the periodic safety reporting.
	Section 7, Section 9.2.3.1.2 • Corrections of typographical or minor errors; unification of terms with the protocol
	Section 9.2.2.1 • Modified the age categorization to align with the summarization in the interim report of the Investigation of Health Status of Recipients Vaccinated First conducted by the Sciences Research Group of the Ministry of Health, Labour and Welfare.
3.0 13-DEC-2021 PPD Ongoing	Section 2.1 • Deleted the categories for duration of safety assessment.
	Section 2.1, Section 2.2, Section 5.4, Section 9.2.3.1.3, Section 10 • Made changes in accordance with the protocol revision concerning subjects with booster vaccination.
	Section 5.4 • Added subgroups for presence/absence of suspected pregnancy/ of lactation (in accordance with the Investigation of Health Status of Recipients Vaccinated First) • Deleted the plan to summarize subjects for presence/absence of pregnancy and of lactation per safety assessment period, in association with the deletion of the duration categories.
	Section 9.2.1.1 • Corrected what subjects should be included in the analyses for tabulation.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
	Section 9.2.2.1 • Added summarization items in accordance with the subgroups defined. • Added summarization of data for presence/absence of allergy • Added summarization items concerning initial immunization and booster vaccination.
	Section 9.2.3.1.1 • Deleted unnecessary analysis plans. • Deleted the plan to summarize relevant subjects for each category of duration of safety assessment, in association with the deletion of the duration categories.
	Section 9.2.3.1.2 • Deleted the plan to summarize relevant subjects for each category of duration of safety assessment, in association with the deletion of the duration categories. • Minor corrections
	Section 9.2.3.2.1 • Deleted the plan to summarize relevant subjects for each category of duration of safety assessment, in association with the deletion of the duration categories.
	Section 9.2.3.3 • Editorial revisions
	Section 10 • Updated to include a tabulated list of non-serious adverse events • Deleted a listing of subjects (Safety Analysis Set) • Updated to include tabulated lists of adverse reactions and adverse events after booster vaccination and information on COVID19.
4.0 07-JUN-2022	Cover page • Renewed Pfizer's logo in accordance with the protocol.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
PPD Ongoing	Section 2.1 • Clarified the definition of the starting point to calculate the duration of safety assessment. • Added a statement that the booster vaccination concerned should be regardless of whether it is with this product or not.
	Section 5.4, Section 9.2.2.1, Section 9.2.3.1.1, Section 9.2.3.2.1, Section 9.2.3.4, Section 10 • Editorial revisions
	Section 5.4 • Defined the presence/absence of renal/hepatic impairment and added a summarization plan for the subgroups concerned.
	Section 8 • Added how to handle the data of subjects lacking information on booster (third) vaccination.
	Section 9.2.3.2.3 • Defined the Safety Specification and added an analysis plan for it.
	Section 9.2.3.3 • Editorial revisions associated with the changes in the summarization scheme.
	Section 9.2.3.4 • Updated the analysis plan to include determination of risk ratios adjusted for sex and age. • Added subgroup analyses regarding age, presence/absence of pregnancy, renal impairment, and hepatic impairment.
	Section 10 • Updated to include lists of subjects in the scope of the safety specification (Section 9.2.3.2.3) and of subjects included in additional subgroups (Section 9.2.3.4) . • Updated to include a listing of subjects who received one dose of vaccination for the initial immunization during the Investigation of Health Status of Recipients Vaccinated First and received a second dose during the observation period of this study

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
5.0 09-NOV-2022 PPD All data fixed	Section 8 • Added how to handle the data lacking information on date. • Changed the name of the tabulated list.
	Section 9.2.2.1 • Added "unknown" as a category for summarization of presence/absence of booster (third) vaccination.
	Section 9.2.3.2.1 • Editorial revisions
	Section 9.2.3.2.2 • Added the analysis plan for onset time of serious adverse events.
	Section 10 • Added a list of information about COVID-19 in subjects who experienced serious adverse events (COVID-19) • Changed the name of a list to "Excluded data in subjects lacking information on booster (third) vaccination" (Section 8) • Added a list of "Details of reason for discontinuation in subjects who discontinued before booster (third) vaccination"

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
6.0 05-DEC-2022 PPD All data fixed	Section 9 • Added a statement that data collected from the Investigation of Health Status of Recipients Vaccinated First will be reviewed according to Pfizer's coding rules, and how the data will be handled in the analysis.
	Section 9.2.3.2.3 • Changed the MedDRA version to 25.1 for PTs.
	Section 11.1 • Deleted the title of the figure.

2. INTRODUCTION

This document describes the statistical analysis plan for the non-interventional study entitled "General Investigation of COMIRNATY Intramuscular Injection (Follow-up Study for Subjects [Healthcare Professionals] Who are Vaccinated at an Early post-Approval Stage)". In this SAP, citations from the corresponding protocol are indicated in *italics*.

2.1. Study Design

[Vaccination Recipients Included in this Study]

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

- Subjects who participated in the Investigation of Health Status of Recipients Vaccinated First and have provided written informed consent to continued participation in this study.

[Exclusion Criteria]

There are no exclusion criteria for this study.

[Safety Evaluation Period]

Subjects in this study will be followed for 11 months from the day following 28 days after the final vaccination of the initial immunization with this product (i.e., the end of the observation period in Investigation of Health Status of Recipients Vaccinated First).

Subjects who discontinued this study will be followed until the day of discontinuation, and those who received booster vaccination (regardless of whether it is with this product or not) will be followed until the day before the booster vaccination.

[Planned Study Period]

The planned period covered by this study is as follows.

- Investigation period: From the day following the day of completion of the observation period for the first subject who has completed the observation period in the Investigation of Health Status of Recipients Vaccinated First to the end of the observation period for the last subject investigated in this study (scheduled from March 2021 to August 2022)

2.2. Study Objective

In this investigation, the healthcare professionals who are vaccinated with this product early after the marketing approval of this product (participants in the Investigation of Health Status of Recipients Vaccinated First conducted by the Science Research Group of the Ministry of Health, Labour and Welfare) will be followed for 11 months from the day following 28 days after the final vaccination of the initial immunization with this product (end date of observation period in Investigation of Health Status of Recipients Vaccinated First) to 12 months after the final vaccination of the initial immunization whit this product, information on serious adverse events and COVID19 observed during the follow-up period will be collected.

If booster vaccination isn't conducted, the long-term safety after the initial immunization of this product during the follow-up period will be assessed.

In booster vaccination is conducted, the long-term safety after the initial immunization of this product up to the day before booster vaccination will be confirmed, and information on serious adverse events and COVID-19 will continuously obtained after booster vaccination.

2.3. Safety Specifications

2.3.1. Important potential risks

Important potential risks include vaccine-associated enhanced disease (VAED) and vaccine-associated enhanced respiratory disease (VAERD).

2.3.2. Important missing information

Information on the safety following vaccination to pregnant women or nursing mothers is missing.

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses for Japan Periodic Safety Update Report (J-PSUR) will be conducted on a regular basis. Interim analyses for purposes other than J-PSUR will also be conducted, as necessary. At the time of an interim analysis, only necessary items selected from the full analysis items defined in this SAP will be analyzed. A final analysis will be conducted to support the application of reexamination. At the time of final analysis, the full items defined in this SAP will be analyzed.

4. HYPOTHESES AND DECISION RULES

Because of the non-confirmatory nature of this study, no hypothesis tests will be performed in this study.

4.1. Statistical Hypotheses

No hypothesis tests will be performed.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is the full analysis set that is as close to all subjects who have given consent to participate in this study as possible. Specifically, the safety analysis set consists of all subjects who gave consent to participate in this study except those who meet at least one or more following conditions:

1. No case report form is collected. (Indicated as “CRF not collected” in the study report.)
2. Any violation or deficiency is found concerning the study contract. (Indicated as “Contract violation/deficiency” in the study report.)
3. The registration does not meet all the requirements. (Indicated as “Invalid registration” in the study report.)
4. No information is reported for adverse events. – No report after participation in this study (Indicated as “No AE information” in the study report.)

Details of each criterion follow the Guidance for Adoption/Rejection Criteria for Analysis Populations and Handling of Data in Drug Use-Results Surveys.

5.2. Effectiveness Analysis Set

Not applicable.

5.3. Other Analysis Sets

Not applicable.

5.4. Subgroups

Subgroup analyses of safety will be performed with respect to the following recipient characteristics (factors). The subgroups in each categorization are indicated in the squared brackets [] with the reference for risk ratio/difference being underlined.

- Sex [male, female]

- Age [≤55 yrs., ≥55 yrs.], [≤65 yrs., ≥65 yrs.]
- Past history of allergy [absent, present]

In addition, subgroup analyses of safety with respect to other factors indicated below will be performed, as necessary:

- Suspected pregnancy/Lactation (women only, for each dose number for initial immunization) [absent, present]
- Pregnancy (women only) [absent, present]
- Lactation (women only) [absent, present]
- History of other vaccination (except boosts) [absent, present]
- Renal impairment [absent, present]
- Hepatic impairment [absent, present]

Presence/absence of renal/hepatic impairment should be determined according to "Attachment: Procedure to Extract Patients with Hepatic/Renal Impairment in Post-Marketing Investigations".

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Serious adverse events or serious adverse reactions: Adverse events/reactions considered by the physician to be serious

Events in the scope of the safety specification will be specified separately.

6.2. Efficacy Endpoints

Not applicable.

6.3. Other Endpoints

Not applicable.

6.4. Covariates

No covariates or potential covariates have been identified for the safety or effectiveness of this product on the basis of currently available data including those from clinical studies.

7. HANDLING OF MISSING DATA

If the action taken for an AE or outcome of an AE is missing, they will be treated as having a value of "unknown" for data tabulation. If the causality of an AE is missing, the event will be treated as "causally related" for data tabulation.

Cleaning-uncompleted data will be in principle handled as follows:

- Items for which relevant data are missing: For both tabulation and listing, their values will be handled as missing data (or they will be treated as "unknown" for a categorical variable).
- Items for which relevant data are inconsistent: For both tabulation and listing, their values will be handled as missing data. In addition, a list will be presented separately for details of data-handling.
- Items with no signature: For both tabulation and listing, any record in a CRF with no signature of a contract physician (including when the CRF is signed only by individuals other than contract physicians) will be handled as missing data. A record in the CRF will be regarded as having no signature if the date is missing despite presence of a space for date or an inconsistent date (e.g., a future date) is filled in.

8. HANDLING OF DATA WITH MISSING INFORMATION ON BOOSTER (THIRD) VACCINATION

If for a subject it cannot be determined whether booster (third) vaccination was given or not or although booster vaccination was confirmed to have been given but its date is unknown, the subject's data covered by CRF Booklet 02 (i.e., data from the day following 6 months after the final vaccination with this product for the initial immunization to 12 months [52 weeks] following the final vaccination with this product for the initial immunization) will be excluded from the safety analysis. Data excluded should be those from the next day of completion (termination) of observation (final observation day) for CRF Booklet 01 (or for data lacking information of date, data collected in CRF Booklet 02 should be excluded), and a separate list of excluded data will be prepared.

9. STATISTICAL METHODS AND ANALYSES

Copied data from the Investigation of Health Status of Recipients Vaccinated First that have been stored in the database for this study will be appropriately reviewed according to Pfizer's coding rules, as necessary, e.g., when multiple pieces of information are contained in the same field. For tabulations and listings defined in this SAP, data after review will be used; data given the "Out of Scope for Coding" status will not be included in those tabulations or listings.

9.1. Statistical Methods

9.1.1. Continuous variables

For continuous variables, summary statistics (n, mean, standard deviation [SD], median, maximum, minimum) will be presented.

9.1.2. Categorical variables

For categorical variables, subjects included in each category will be calculated in terms of frequency (such as n) and proportion.

9.1.3. Binary variables

For binary variables, subjects included in each binary category will be calculated in terms of frequency and proportion. When a confidence interval (CI) is determined for a proportion, the two-sided 95% CI (exact method) will be determined.

When a comparison for proportion is made between subgroups, the risk ratio and its 95% CI will be calculated. They will also be presented graphically (See Appendix 1).

9.2. Statistical Analyses

9.2.1. Subject description

9.2.1.1. Constitution

Among CRF-collected subjects, those included in the safety analysis set will be tabulated. In addition, subjects excluded from the safety analysis set, and those excluded from the safety analysis set for each reason will be tabulated.

9.2.1.2. Vaccination discontinuation and dropouts

Using the safety analysis set, subjects who discontinued this study will be summarized in terms of n and proportion. Summarization will also be performed by reason of discontinuation for both n and proportion. Reasons for discontinuation are categorized into adverse events, death, lost to follow-up, consent withdrawal, or other.

9.2.1.3. Subjects excluded from analysis

Subjects excluded from the safety analysis set will be listed in tabular form with their reasons for exclusion.

9.2.2. Subject characteristics and treatment history

9.2.2.1. Subject characteristics

Using the safety analysis set, characteristics of vaccinated subjects collected in the Investigation of Health Status of Recipients Vaccinated First will be summarized according to Section 8.1, with respect to the following factors:

- Sex [male, female]
- Age (continuous)

- Age (categorical) [≥0 to <10 yrs., ≥10 to <20 yrs., ≥20 to <30 yrs., ≥30 to <40 yrs., ≥40 to <50 yrs., ≥50 to <60 yrs., ≥60 to <70 yrs., ≥70 to <80 yrs., ≥80 to <90 yrs., ≥90 yrs.]
- Past history [absent, present]
- Complications [absent, present]
- Allergy [absent, present]
- Suspected pregnancy/Lactation (women only, for each dose number for initial immunization) [absent, present]
- Pregnancy (women only) [absent, present]
- Lactation (women only) [absent, present]
- Duration of safety assessment (days)
- Number of doses for initial immunization during the study period for the Investigation of Health Status of Recipients Vaccinated First [1 dose, 2 doses]
- Dose interval for initial immunization (recipients of two doses only) (day of 2nd dose − day of 1st dose)
- Booster (third) vaccination [absent, present (this product, other), unknown]

Using the safety analysis set, a breakdown of subjects according to each of the following factors will be presented in terms of n and proportion by system organ class (SOC) and preferred term (PT):

- Past history
- Complications

9.2.3. Safety analyses

The listings will include all relevant events reported in this study.

9.2.3.1. Adverse reactions

9.2.3.1.1. Serious adverse reactions

Serious adverse reactions will be summarized by SOC and PT in terms of n and proportion. Multiple adverse reactions of the same PT occurring in the same vaccine recipient will be counted only once.

9.2.3.1.2. Details of serious adverse reactions

Serious adverse reactions will be summarized in terms of n and proportion by each of the following factors:

- Action taken (additional treatment) [present, absent]
- Outcome [not recovered, recovered with sequelae, improved, resolved/recovered, death, unknown]
- Severity [mild, moderate, severe, life-threatening]
- Batch number

Subjects who experienced multiple adverse reactions with the same PT will be summarized in the manner described below in terms of summarization of n:

- Days to onset: The days to the first onset will be adopted.
- Action taken (additional treatment): If multiple actions were taken for adverse reactions occurring in the same subject with the same PT, only one kind of action will be adopted with “present” being given priority over “absent”.
- Outcome: The outcome for the last reaction will be adopted.
- Severity: If the same subject experienced multiple adverse reactions with the same PT in different severities, the subject will be handled as having experienced an event of one level of severity with “life-threatening”, “severe”, “moderate”, and “mild” being given priority in this order.

9.2.3.1.3. Onset time of serious adverse reactions

Serious adverse reactions will be summarized in terms of n and proportion (denominator = the number of subjects vaccinated) by the time of first onset [from the day after 28 days following the last dose for initial immunization with this product to 3 months after the last dose for initial immunization with this product, from the day after 3 months following the last dose for initial immunization with this product to 6 months after the last dose for initial immunization with this product, from the day after 6 months following the last dose for initial immunization with this product to 12 months after the last dose for initial immunization with this product] and by SOC and PT. For subjects with booster vaccination, only events that occurred by the day before booster dosing will be included.

9.2.3.1.4. Occurrence of serious adverse reactions in subjects excluded from the safety analysis set

Using data from CRF-collected subjects, serious adverse reactions reported during the entire evaluation period in subjects excluded from the safety analysis set will be identified and presented in tabular form. The adverse reactions identified will also be summarized in terms of n by SOC and PT.

9.2.3.2. Adverse events

9.2.3.2.1. Serious adverse events

Serious adverse events will be summarized by SOC and PT in terms of n and proportion. Multiple adverse events of the same PT occurring in the same vaccine recipient will be counted only once.

9.2.3.2.2. Onset time of serious adverse events

Serious adverse events will be summarized in terms of n and proportion (denominator = the number of subjects vaccinated) by the timing of first onset [from the day after 28 days following the last dose for initial immunization with this product to 3 months after the last dose for initial immunization with this product, from the day after 3 months following the last dose for initial immunization with this product to 6 months after the last dose for initial immunization with this product, from the day after 6 months following the last dose for initial immunization with this product to 12 months after the last dose for initial immunization with this product] and by SOC and PT. For subjects with booster vaccination, only events that occurred by the day before booster dosing will be included.

9.2.3.2.3. Safety specification

For the following elements in the safety specification, subjects who experienced a relevant event will be listed in tabular form:

- VAED and VAERD
  Definition: Any event coded as one of the following PTs:

  Vaccine associated enhanced respiratory disease, Vaccine associated enhanced disease, Dyspnoea, Tachypnoea, Hypoxia, COVID-19 pneumonia, Respiratory failure, Acute respiratory distress syndrome, Cardiac failure, Cardiogenic shock, Acute myocardial infarction, Arrhythmia, Myocarditis, Vomiting, Diarrhoea, Abdominal pain, Jaundice, Acute hepatic failure, Deep vein thrombosis, Pulmonary embolism, Peripheral ischaemia, Vasculitis, Shock, Acute kidney injury, Renal failure, Altered state of consciousness, Seizure, Encephalopathy, Meningitis, Cerebrovascular accident, Thrombocytopenia, Disseminated intravascular coagulation, Chillblains, Erythema multiforme, Multiple organ dysfunction syndrome, Multisystem inflammatory syndrome in children

9.2.3.3. Information about COVID-19

Using the safety analysis set, subjects underwent or not underwent any COVID-19 pathogen test (excluding antibody test) will be summarized. Among tested subjects (except with antibody test), those with each result (positive or negative) will be summarized in terms of n and proportion. Furthermore, positive subjects will be summarized by kind of test in terms of n and proportion, and positive subjects developing COVID-19 will be summarized by n and proportion. In addition, subjects with severe COVID-19 will be summarized in terms of n and proportion (denominator = the number of subjects with COVID-19) with severe cases being defined as any of the following actions taken during the period from disease onset to the outcome date:

- Admission to an ICU
- Use of mechanical ventilation
- Use of ECMO

Subjects underwent or not underwent antibody test, as well as those with each result (positive or negative) will also be summarized in terms of n and proportion.

9.2.3.4. Subgroup analyses

Subjects with at least one serious adverse reaction will be summarized in terms of n and proportion by each factor defined in Section 5.4. According to Section 9.1.3, risk ratios between subgroups will be determined and graphically presented for the proportion of subjects with any serious adverse reactions. For all factors except sex and age, risk ratios adjusted for sex and age (<65 yrs., ≥65 yrs.) will also be determined using the Mantel-Haenszel method, and graphically presented. If there is a category with only <5 subjects and recategorization has been determined to be infeasible after consideration, however, the risk ratio for such category may not be determined.

For each of the following factors among specified in Section 5.4, subjects who had serious adverse reactions will be summarized by SOC and PT in terms of n and proportion.

- Age [<65 yrs., ≥65 yrs.]
- Pregnancy (women only) [absent, present]
- Renal impairment [absent, present]
- Hepatic impairment [absent, present]

Serious adverse events will also be analyzed in the same manner.

9.2.3.5. Exploratory analyses

Additional analyses may be performed, as necessary. Exploratory analyses will be reported only when results obtained provide an important interpretation.

10. LISTINGS

Tabulated lists will be presented for the following subjects or items:

- Subjects included in the study
  In addition, separated lists will be presented for the following subjects included in the study:
    - Elderly (≥65 yrs.)
    - Subjects reported as “present” for pregnancy
    - Subjects reported as “present” for renal impairment
    - Subjects reported as “present” for hepatic impairment
    - Subjects who experienced VAED or VAERD (See Section 9.2.3.2.3)

    - Subjects who received one dose of vaccination for initial immunization during the study period of the Investigation of Health Status of Recipients Vaccinated First and received the second dose (regardless of whether it is with this product or not) during the observation period of this study

- Subjects who experienced serious adverse reactions
- Subjects who experienced serious adverse reactions after booster (third) vaccination
- Subjects who experienced serious adverse events
- Subjects who experienced non-serious adverse events
- Information about COVID-19 in subjects who experienced serious adverse events of COVID-19
- Subjects who experienced serious adverse events after booster (third) vaccination
- Subjects excluded from the safety analysis set who experienced serious adverse reactions
- Information about COVID-19 cases occurring after booster (third) vaccination
- Excluded data in subjects lacking information on booster (third) vaccination
- Details of reason for discontinuation in subjects who discontinued before booster (third) vaccination

Documents required for application of re-examination (of which forms are presented in PSEHB/PED Notification No. 1128-2 issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated November 28, 2017) will also be prepared.

In addition, documents required for the periodic safety reporting (of which forms are presented in PSEHB/PED Notification No. 1128-5 issued jointly by the Director of the Pharmaceutical Evaluation Division and the Director of the Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated November 28, 2017) will be prepared for the purpose of the reporting.

11. APPENDICES

11.1. Appendix 1: Example of Tables and Figures of Risk Ratios for Adverse Reactions Occurring in Subgroups

Event name: Increased XXX	Category 1	Category 2	Risk Ratio (RR)	
	n/N (%)	n/N (%)	RR	95% CI
Sex (male vs. female)	18/2220 (0.8)	3/1099 (0.3)	2.97	(0.88-10.06)
Age (≥65 yrs. vs. <65 yrs.)	19/2788 (0.7)	2/531 (0.4)	1.81	(0.42-7.74)
Diagnosis (disease A vs. disease B)	3/221 (1.4)	18/3098 (0.6)	2.34	(0.69-7.87)
Duration of disease (<1 yr. vs. ≥1 yr.)	9/771 (1.2)	7/866 (0.8)	1.44	(0.54-3.86)
Concomitant use of Drug A (present vs. absent)	9/798 (1.1)	12/2521 (0.5)	2.37	(1.00-5.60)
Pretreatment with Drug A (present vs. absent)	1/148 (0.7)	20/3171 (0.6)	1.07	(0.14-7.93)
Complication of Disease B (present vs. absent)	16/1614 (1.0)	5/1703 (0.3)	3.38	(1.24-9.20)
Past history of Disease B (present vs. absent)	7/674 (1.0)	14/2643 (0.5)	1.96	(0.79-4.84)
Hepatic impairment (present vs. absent)	0/80	18/2056 (0.9)		
Renal impairment (present vs. absent)	1/140 (0.7)	17/2004 (0.8)	0.84	(0.11-6.28)

Incidence Proportions and Risk Ratios for Adverse Reaction XXXX