Non-Interventional Study Protocol

C4591019

Special Investigation of COMIRNATY Intramuscular Injection (Investigation of Patients with Underlying Disease Considered to be at High Risk of Aggravation of COVID-19)

Statistical Analysis Plan

Version: 6.0

Author: PPD

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1. REVISION HISTORY

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
1.0 17-MAR-2021 PPD Before Enrollment	First edition
2.0 11-JUN-2021 PPD Ongoing	Section 3, Section 5.4, Section 8.2.3.1.1 • Corrections of typographical or minor errors; unification of terms
	Section 5.4 • Revised the analysis plan in such a way that data for presence/absence of pregnancy and of lactation are to be summarized separately to align with the CRF.
	Section 8.2.3.3 • Updated the interim analysis plan to include analyses for local/systemic reactions.
3.0 04-AUG-2021 PPD Ongoing	Section 2.1 • Changes to align with the protocol revision based on the extended age range for vaccination
	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 8.2.1.2, Section 8.2.3.1.3, Section 8.2.3.3.2 • Corrections of typographical or minor errors; unification of terms with the protocol
	Section 8.2.2.1 • Modified the age categorization to align with the summarization in the interim report of the Survey of Health Status in Early Vaccination Recipients conducted by the Sciences Research Group of the Ministry of Health, Labour and Welfare.
4.0 07-DEC-2021 PPD	Section 5.1 • Updated the definition of the safety analysis set (to include an exclusion criterion for out-of-scope underlying diseases)

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
Ongoing	Section 5.4 • Updated the definition of the subgroup in terms of presence/absence of pregnancy and for presence/absence of lactation (deleted the phrase "for each evaluation period" from the definition)
	Section 8.2.1.1 • Revised the summarization plan for patient disposition.
	Section 8.2.2.1 • Added summarization of data for presence/absence of pregnancy and for presence/absence of lactation.
	Section 8.2.3.1.1 • Deleted unnecessary analysis plans.
	Section 8.2.3.1.3 • Minor corrections
	Section 8.2.3.3.1, Section 8.2.3.3.2 • Added summarization of any local (systemic) reaction and of events of any severity to the analyses by highest severity and onset time. • Added summarization of any local (systemic) reactions to the analyses of onset time. • Updated the analysis plan for onset time to specify how to handle cases in which an event occurring after the first vaccination is still ongoing at the time of the second vaccination. • Corrected the content of interim analyses
	Section 9 • Deleted unnecessary lists. • Made a change from "List of patients with a specific adverse event" to "List of health observation diaries".
5.0 13-DEC-2021	Section 8.2.2.1 • Added summarization of data for presence/absence of allergy

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
PPD Ongoing	Section 8.2.3.4 • Editorial revisions
6.0 25-Mar-2022 PPD Enrollment Complete	Section 5.4 • Added the age category of "<15 years", with a change from the category of "<65 years" to the category of "≥15 to <65 years".
	Section 8.2.2.2 • Modified the categorization of the vaccination interval from the first vaccination to include the category of "21 days", with a change from the category of "≥21 days" to that of "≥22 days".
	Section 8.2.3.1.3 • Deleted the summarization plan for the entire evaluation period.
	Section 8.2.3.1.4 • Editorial revisions
	Section 8.2.3.2.4 • Added a definition of and analysis plan for the safety specifications.
	Section 8.2.3.3.1, Section 8.2.3.3.2 • Updated the analysis plan by onset time to include graphical presentation of the incidence of events of each severity.
	Section 8.2.3.3.3 • Added an analysis plan for the development of specific adverse events in patients excluded from the safety analysis set.
	Section 8.2.3.4 • Editorial revisions associated with changes in the summarization scheme.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
	Section 8.2.3.5 • Updated the analysis plan to include determination of risk ratios adjusted with sex and age. • Updated the analysis plan for "the development of any local reactions or systemic reactions (including pyrexia)" to include only severe events. • Added subgroup analyses regarding age, presence/absence of pregnancy, renal impairment, and hepatic impairment.
	Section 9 • Updated to include tabulated lists of patients in the scope of the safety specification (Section 8.2.3.2.4) and of patients included in additional subgroups (Section 8.2.3.5). • Updated to include a tabulated list of health observation diaries for patients excluded from the safety analysis set.

2. INTRODUCTION

This document describes the statistical analysis plan for the non-interventional study entitled "Special Investigation of COMIRNATY Intramuscular Injection (Investigation of Patients with Underlying Disease Considered to be at High Risk of Aggravation of COVID-19)". In this SAP, citations from the corresponding protocol are indicated in *italics*.

2.1. Study Design

Vaccination Recipients Included in the Study

All of the following inclusion criteria must be met for a vaccination recipient to be eligible for the study:

1. *The recipient can understand the content of this study and record their symptoms in their health observation diary, and the recipient themselves (or their parent or legal guardian in the case of minors) has provided written informed consent to participating in the study.*

2. *The recipient has an underlying disease considered to be at high risk of aggravation of COVID-19 at the time of vaccination with this product*

   Underlying diseases considered to be at high risk of aggravation of COVID-19 are based on the population indicated by the Ministry of Health, Labour and Welfare for priority vaccination. In principle, inclusion of a vaccination recipient in this study will be determined by the physician by

confirming the eligibility criteria through medical interview, etc. after the vaccination recipient fills in the questions about the underlying disease in the preliminary examination sheet.

[Indications]

Prevention of infection with SARS-CoV-2

[Dosage and Administration]

The product is diluted with 1.8 mL of Japanese Pharmacopoeia physiological saline and administered intramuscularly at a dose of 0.3 mL 2 times in total, usually at a 3-week interval.

[Possible Vaccination Recipients]

Those aged 12 years or older will be vaccinated with this product.

[Vaccination Interval]

If 3 weeks or more have passed since the first vaccination, the second vaccination should be given as soon as possible.

[Exclusion Criteria]

No exclusion criteria have been set for this study.

[Target Sample Size]

In this study, the target sample size for the safety analysis set is 1,000 patients.

[Rationale for Sample Size]

Considering the possible timing of vaccination for individuals with underlying diseases who are considered to be at high risk of aggravation of COVID-19, the timing of conducting this study may be limited. In addition, this study is expected to place a large burden on study sites, because the sites are required to provide vaccination recipients with information for obtaining informed consent, to request them to keep a health observation diary, and to collect the diaries from them. Considering the feasibility, the target sample size was set at 1,000 patients.

If data are collected from 1,000 patients who have received at least one vaccination with this product, it is possible to observe an event that occurs with a true probability of 0.3% in at least one patient with a probability of 95%. In addition, from the results of the safety analysis in at-risk populations in Study C4591001, it is expected that the safety profile of individuals aged 56 years or older should not differ from that of patients with underlying disease that are considered to be at high risk of aggravation of COVID-19.

The safety data obtained so far from individuals aged 56 years or older in Study C4591001 indicate that the incidence of severe adverse events occurring after vaccination with this product ranged from 0.1%

(vomiting and diarrhoea) to 2.8% (fatigue). It may therefore be possible to confirm these events by collecting safety information from 1,000 subjects.

[Safety Evaluation Periods]
Evaluation for the entire period: The entire evaluation period for each patient is from the day of the first vaccination (Day 1) with this product to the end of the observation period (i.e., the day when the patient first visits the site following the last vaccination, or when patient information is last collected).

Evaluation for the first vaccination 1: From the day of the first vaccination (Day 1) to the day before the second vaccination; for subjects vaccinated only once, the period ends at the end of the observation period (i.e., the day when the patient first visits the site following the first vaccination, or when patient information is last collected).

Evaluation for the second vaccination: From the day of the second vaccination (Day 1) to the end of the observation period (i.e., the day when the patient first visits the site on or after Day 28 [with Day 1 being the day of the second vaccination], or when patient information is last collected).

[Planned Study Period]

This study is planned to be conducted for the periods below:

- *Survey period: From the date of the first vaccination 1 for the first registered patient to the end of the observation period for the last registered patient (expected to be from April 2021 to December 2021)*
- *Registration period: From the date of the first vaccination for the first registered patient to the registration date for the last registered patient (expected to be from April 2021 to October 2021)*

Registration will be terminated even before the end of the expected registration period if the number of registered patients reaches the target sample size.

2.2. Study Objective

The objective of this study is to collect information on adverse events and COVID-19 cases occurring after vaccination with this product and confirm the product's safety in patients with underlying disease considered to be at high risk of aggravation of COVID-19 after marketing approval of this product.

2.3. Safety Specifications

2.3.1. Important identified risks

Important identified risks include shock and anaphylaxis.

2.3.2. Important potential risks

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

2.3.3. 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 for this study.

4.1. Statistical Hypotheses

No hypothesis tests will be performed.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SET

5.1. Safety Analysis Set

The safety analysis set is the full analysis set that is as close to all patients vaccinated with this product at least once as possible. Specifically, the safety analysis set consists of all registered or reported patients except those who meet at least one of the 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 vaccination with this product was reported. (Indicated as “No vaccination information” in the study report.)
5. No information is reported for adverse events. — No report after the first vaccination (Indicated as “No AE information” in the study report.)
6. Underlying disease that is out of scope

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 patient characteristics. The subgroups in each categorization are indicated in the squared brackets [] with the reference for risk ratio/difference being underlined.

- Sex [male, female]
- Age at the first vaccination [<55 yrs., ≥55 yrs.], [<15 yrs., ≥15 to <65 yrs., ≥65 yrs.]
- Past history of allergy [absent, present]
- Complications of the underlying disease considered to be at high risk of aggravation of COVID-19 [absent, present]

A list of diseases that should be treated as an underlying disease considered to be at high risk of aggravation of COVID-19 will be presented separately.

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

- Pregnancy (women only) [absent, present]
- Lactation (women only) [absent, present]
- History of other vaccinations (before vaccination with this product, after vaccination with this product) [absent, present]

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse reactions: Adverse events considered by the physician to be causally related to this product
- Adverse events: Adverse events independent of causality
- Serious adverse events or serious adverse reactions: Adverse events/reactions considered by the physician to be serious

- Specific adverse events: Reactogenicity events (local reactions, systemic reactions) collected via the health observation diary

Events included 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 severity of an AE, 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. STATISTICAL METHODS AND ANALYSES

8.1. Statistical Methods

8.1.1. Continuous variables

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

8.1.2. Categorical variables

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

8.1.3. Binary variables

For binary variables, patients 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 of proportion is made between subgroups, the risk ratio and its 95% CI will be calculated. They will also be presented graphically (See Appendix 1).

8.2. Statistical Analyses

8.2.1. Patient description

8.2.1.1. Constitution

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

8.2.1.2. Vaccination discontinuations and dropouts

Using the safety analysis set, patients vaccinated only once (i.e., those who have discontinued vaccination after the first vaccination) will be summarized in terms of n and proportion. Summarization will also be performed by reason of discontinuation for both n and proportion. Similarly, patients withdrawn from this study will be summarized. Reasons for discontinuation are categorized into adverse events, death, lost to follow-up, consent withdrawal, and other.

8.2.1.3. Patients excluded from analysis

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

8.2.2. Patient characteristics and treatment history

8.2.2.1. Patient characteristics

Using the safety analysis set, characteristics of vaccinated patients at the day of the first vaccination 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]
- Complications of the underlying disease considered to be at high risk of aggravation of COVID-19 [absent, present]
- Pregnancy (women only) [absent, present]
- Lactation (women only) [absent, present]

Using the safety analysis set, a breakdown of patients 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

8.2.2.2. Status of vaccination with this product

Using the safety analysis set, the status of vaccination with this product will be summarized by each of the following factors:

- For the first vaccination:
  Injection site [deltoid, other]
- For the second vaccination
  Vaccination interval from the first vaccination (continuous) (= the date of the second vaccination - the date of the first vaccination)
  Vaccination interval from the first vaccination [<21 days, 21 days, ≥22 days]
  Injection site [deltoid, other]

8.2.3. Safety analyses

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

8.2.3.1. Adverse reactions

8.2.3.1.1. All adverse reactions

Adverse reactions reported during the entire evaluation period will be summarized by SOC and PT in terms of n and proportion. If the same vaccinated patient experiences two or more adverse reactions with the same PT, they should be counted only once. Similarly, adverse reactions reported during the evaluation

period for the first vaccination and for the second vaccination will be summarized (For the definition of each safety evaluation period, see Section 2.1). Adverse reactions with the same PT occurring in the same patient will be evaluated and summarized for each evaluation period, but reactions continuing from a period to the other will be counted only for the former period in which the onset date is included.

8.2.3.1.2. Serious adverse reactions

Serious adverse reactions reported during the entire evaluation period will be summarized by SOC and PT in terms of n and proportion. Similarly, serious adverse reactions reported during the evaluation period for the first vaccination and for the second vaccination will be summarized.

8.2.3.1.3. Details of adverse reactions

Adverse reactions reported during the evaluation period for the first vaccination and for the second vaccination will be summarized in terms of n and proportion by each of the following factors:

- Seriousness [serious, non-serious]
- Action taken (modification of the vaccination with this product) [discontinuation, not applicable]
- 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

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

- Seriousness: If the same patient experienced both serious and non-serious adverse reactions with the same PT, the patient will be handled as having experienced a serious event.
- Days to onset: The days to the first onset will be adopted.
- Action taken (modification of the vaccination with this product): If multiple actions were taken for adverse reactions occurring in the same patient with the same PT, only one kind of action will be adopted with “discontinuation” being given priority over “not applicable”.
- Action taken (additional treatment): If multiple actions were taken for adverse reactions occurring in the same patient 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 onset reaction will be used.

- Severity: If the same patient experienced multiple adverse reactions with the same PT in different severities, the patient 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.

8.2.3.1.4. Onset time of adverse reactions

Adverse reactions in the evaluation period for each vaccination (first or second) will be summarized in terms of n and proportion (denominator = the number of patients vaccinated for each dose number) by the time of first onset [Day 1 (= the day of first or second vaccination), Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9-] and by SOC and PT.

8.2.3.1.5. Occurrence of adverse reactions in patients excluded from the safety analysis set

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

8.2.3.2. Adverse events

8.2.3.2.1. All adverse events

All adverse events reported during the entire evaluation period will be summarized by SOC and PT in terms of n and proportion. Similarly, adverse events reported during the evaluation period for the first and second vaccination will be summarized.

8.2.3.2.2. Serious adverse events

Serious adverse events reported during the entire evaluation period will be summarized by SOC and PT in terms of n and proportion. Similarly, serious adverse events reported during the evaluation period for the first and second vaccination will be summarized.

8.2.3.2.3. Non-serious adverse events

Non-serious adverse events reported during the entire evaluation period will be summarized by SOC and PT in terms of n and proportion. Similarly, non-serious adverse events reported during the evaluation period for the first and second vaccination will be summarized.

8.2.3.2.4. Safety specifications

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

- Shock and anaphylaxis
  Definition: Any event coded as one of the following PTs:

  Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock

- 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.

8.2.3.3. Specific adverse events (health observation diary)

8.2.3.3.1. Local reactions

Among events observed during the evaluation period for the first vaccination and for the second vaccination, local reactions (injection site pain, redness, and swelling; each kind and any kind) occurring in the maximum severity in individual patients will be summarized for each severity and for any severity, in terms of n and proportion for each evaluation period. Furthermore, local reactions of each level of severity and of any level of severity will be summarized by onset time [Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8] in terms of n and proportion, and results will be presented graphically. In addition, summary statistics will be presented for onset time of each kind of local reaction and of local reaction of any kind, as well as for duration (= date of resolution − date of first onset) of each local reaction. For an event that was still ongoing at the time of the second vaccination following development after the first vaccination, the date of the second vaccination will be used as the resolution date to determine the duration of the event. For interim analyses, local reactions of the maximum severity will be summarized in terms of n and proportion for each evaluation period in patients including those for whom only health observation diary had been fixed.

8.2.3.3.2. Systemic reactions

Among events observed during the evaluation period for the first vaccination and for the second vaccination, systemic reactions (pyrexia, vomiting, diarrhoea, headache, malaise, chills, myalgia, and arthralgia; each kind and any kind) occurring in the maximum severity in individual patients will be summarized for each severity and for any severity, in terms of n and proportion for each evaluation period. Pyrexia is defined as a body temperature of 37.5°C or higher, and its severity should be determined according to **Table 1**. Furthermore, systemic reactions of each level of maximum severity and of any level of maximum severity will be summarized by onset time [Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8] in terms of n and proportion, and results will be presented graphically. In addition, summary statistics will be presented for onset time of each kind of systemic reaction and of systemic reaction of any kind, as well as for duration (= date of resolution - date of first onset) of each systemic reaction. For an event that was still ongoing at the time of the second vaccination following development after the first vaccination, the date of the second vaccination will be used as the resolution date to determine the duration

of the event. For interim analyses, systemic reactions of the maximum severity will be summarized in terms of n and proportion for each evaluation period in patients including those for whom only health observation diary had been fixed.

Table 1. Severity Categories of Pyrexia

Mild Grade 1	Moderate Grade 2	Severe Grade 3
≥37.5°C; ≤38.4°C	≥38.5°C; ≤38.9°C	≥39.0°C

8.2.3.3.3. Occurrence of specific adverse events in patients excluded from the safety analysis set

Using data from CRF-collected patients, specific adverse events reported in patients excluded from the safety analysis set will be identified, and presented in tabular form. In addition, local reactions (injection site pain, redness, and swelling; each kind and any kind) occurring in the maximum severity in individual patients will be summarized for each severity and for any severity, in terms of n and proportion for each evaluation period. Systemic reactions will also be summarized in the same manner.

8.2.3.4. Information about COVID-19

Using the safety analysis set, patients underwent or not underwent any COVID-19 pathogen test (excluding antibody test) will be summarized. Among tested patients (except with antibody test), those with each result (positive or negative) will be summarized in terms of n and proportion. Furthermore, positive patients will be summarized by kind of test in terms of n and proportion, and positive patients developing COVID-19 will be summarized by n and proportion. In addition, patients with severe COVID-19 will be summarized in terms of n and proportion (denominator = the number of patients with COVID-19) with the severe case 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 ventilator
- Use of ECMO

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

8.2.3.5. Subgroup analyses

Patients with at least one adverse reaction will be summarized in terms of n and proportion by each factor defined in Section 5.4. According to Section 8.1.3, risk ratios between subgroups will be determined and graphically presented for the proportion of patients with any 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 patients and re-

categorization has been determined to be infeasible after consideration, however, the risk ratio for such category may not be determined.

Similar analyses will be performed for patients with any serious adverse reactions, any serious adverse events, severe local reaction of any type or severe systemic reaction of any type (including pyrexia), and severe pyrexia.

For each of the following factors among specified in Section 5.4, patients who had adverse reactions and severe adverse reactions during the entire evaluation period will be summarized by SOC and PT in terms of n and proportion. In addition, among events reported during the evaluation period for the first vaccination and for the second vaccination, local reactions (injection site pain, redness, and swelling; each kind and any kind) occurring in the maximum severity in individual patients will be summarized for each severity and for any severity, in terms of n and proportion for each evaluation period. Systemic reactions will also be summarized in the same manner.

- Age [<15 yrs., ≥15 to <65 yrs., ≥65 yrs.]
- Pregnancy (women only) [absent, present]
- Renal impairment [absent, present]
- Hepatic impairment [absent, present]

For determination of renal/hepatic impairment, events specified as an underlying disease considered to be at high risk of aggravation of COVID-19 will be used.

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9. LISTINGS

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

- Patients included in the study
  In addition, separated lists will be presented for the following patients included in the study:
    - Children (<15 yrs.)
    - Elderly (≥65 yrs.)
    - Patients reported as “present” for pregnancy
    - Patients reported as “present” for renal impairment (as an underlying disease considered to be at high risk of aggravation of COVID-19)

  - Patients reported as "present" for hepatic impairment (as an underlying disease considered to be at high risk of aggravation of COVID-19)
  - Patients who experienced shock or anaphylaxis (Section 8.2.3.2.4)
  - Patients who experienced VAED or VAERD (Section 8.2.3.2.4)
- Patients who experienced adverse events
- Patients who experienced adverse reactions
- Patients excluded from the safety analysis set who experienced adverse reactions
- Patients who experienced serious adverse reactions
- Patients who experienced serious adverse events
- Health observation diaries
- Health observation diaries in patients excluded from the safety analysis set

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.

10. APPENDICES

10.1. 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