Non-Interventional Study Protocol

C4591057

COMIRNATY Intramuscular Injection for 6 Months to 4 Years Old(monovalent: Omicron XBB.1.5) Special Investigation for Booster Immunization in Children Aged 6 Months to 4 Years

Statistical Analysis Plan

Version: 2.0

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1. REVISION HISTORY

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
1.0 08-DEC-2023 PPD Before Enrollment	First edition
2.0 14-JUN-2024 PPD Enrollment Complete	• Section 8.2.1.1 Changed the participants included in the analyses from "CRF-collected participants" to "CRF-fixed participants" and deleted the analyses of CRF-uncollected participants. • Section 8.2.2.2 Added summarization of the dose interval between the initial immunization (third vaccination) and the fourth vaccination. • Section 8.2.3.5 Deleted the subgroup analysis regarding serious adverse events from the plan because it was an erroneous description.

2. INTRODUCTION

This document describes the statistical analysis plan for the special investigation of COMIRNATY Intramuscular Injection for 6 months to 4 years old (monovalent: Omicron XBB.1.5) (hereinafter referred to as this product). In this SAP, citations from the corresponding protocol are indicated in *italics*.

2.1. Study Objective

To collect information on adverse events, reactogenicity events (local reactions and systemic reactions), and COVID-19 that occur subsequent to the fourth vaccination with this product in children aged 6 months to 4 years who received the first booster immunization with this product (fourth vaccination with this product) after the initial immunization under actual use, and to confirm its safety in the early stage.

2.2. Study Design

2.2.1. Setting

Vaccinated participants must meet all of the following criteria to be eligible for inclusion in the study.

- *Participants who are 6 months to 4 years old at the time of the fourth vaccination with this product.*

- *Participants who are receiving the first booster immunization with this product (fourth vaccination with this product) after the initial immunization.*

- *Participants for whom written consent was obtained from their legally acceptable representatives (parents or legal guardians) regarding their participation in the study upon understanding the explanatory document describing the content of this study, including that they will be asked to record participant's symptoms in the health observation diary.*

2.2.2. Exclusion criteria

There are no exclusion criteria for this study.

2.2.3. Method of administration

[Indications]

Prevention of infection with SARS-CoV-2

[Dosage and administration]

This product is diluted with 2.2 mL of Japanese Pharmacopoeia physiological saline. For initial immunization, participants are vaccinated intramuscularly at a dose of 0.2 mL 3 times in total. The second dose is usually given at a 3-week interval, and the third dose is given after at least 8 weeks have passed since the second vaccination. For booster immunization, participants are vaccinated intramuscularly at a dose of 0.2 mL.

[Precautions regarding dosage and administration (booster immunization)]

Participants: Those aged 6 months to 4 years with a history of previous vaccination with SARS-CoV-2 vaccines for initial immunization or booster immunization. Based on the state of SARS-CoV-2 pandemic and individual background factors, etc., the necessity of booster immunization should be determined in consideration of benefits and risks.

Vaccination interval: Generally, participants can receive vaccination after at least 3 months have passed since the previous SARS-CoV-2 vaccination.

2.2.4. Observation period

The observation period will be from the date of the fourth vaccination with this product (Day 1) to 28 days after the fourth vaccination. However, for those who withdraw from the study, information up to the time of withdrawal will be collected.

2.2.5. Tabulation period

The tabulation period will be the same as the observation period.

2.2.6. Safety specifications

[Important identified risks]

- *Shock, anaphylaxis*
- *Myocarditis, pericarditis*

[Important potential risks]

- *Vaccine-associated enhanced disease (VAED) and vaccine-associated enhanced respiratory disease (VAERD)*
- *Guillain-Barre syndrome*

2.2.7. Planned sample size and its rationale

60 participants will be collected as the participants to be included in the safety analysis set.

The target sample size (safety analysis set) was set to be 60 participants based on feasibility. If 60 participants can be collected, an adverse event that occurs with a true incidence of 3% can be observed in at least 1 participant with a probability of 83%, which would make it possible to understand trends in incidence of reactogenicity events.

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. At the time of an interim analysis, only necessary items for J-PSUR 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.

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 participants who have received the fourth vaccination with this product as possible. Specifically, the safety analysis set consists of all participants who have been registered or reported 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 the inoculation of the target vaccine (Indicated as "No information on inoculation" in the study report)
5. No information is reported for adverse events. – No report after the fourth vaccination (Indicated as "No AE information" in the study report.)

Details of each criterion follow the latest 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 vaccinated participant characteristics (factors):

- Sex [male, female]
- Age at the fourth vaccination [6 months to <2 years, 2 years to ≤4 years]
- Past history of allergy [absent, present]
- Past history of SARS-CoV-2 infection [absent, present]

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

- Hepatic impairment [absent, present]
- Renal impairment [absent, present]
- History of other vaccination (before and after vaccination with this product) [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 Surveillances."

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse reactions: Adverse events considered by the physician to be causally related
- Adverse event: Any untoward and unintended sign or symptom occurring after vaccination with this product, regardless of causal relationship
- Serious adverse events or adverse reactions: Adverse events or reactions considered by the physician to be serious
- Reactogenicity events: Local and systemic reactions collected in the health observation diary
- Safety specifications: Important identified risks, important potential risks, and important missing information described in the Risk Management Plan. The safety specifications to be investigated in this study are listed below.

  [Important identified risks]

  - *Shock, anaphylaxis*
  - *Myocarditis, pericarditis*

  [Important potential risks]

  - *Vaccine-associated enhanced disease (VAED) and vaccine-associated enhanced respiratory disease (VAERD)*
  - *Guillain-Barre syndrome*

The definition of each safety specification event will be based on the definitions in the Risk Management Plan or Periodic Benefit-Risk Evaluation Report (PBRER) as of the database release (or J-PSUR due date).

6.2. Effectiveness Endpoints

Not applicable.

6.3. Other Endpoints

Not applicable.

6.4. Covariates

No 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 seriousness of an adverse event, action taken for an adverse event, or outcome of an adverse event is missing, the event will be treated as having a value of "unknown" for data tabulation. If the causality of an adverse event 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.

8. STATISTICAL METHODS AND ANALYSIS

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, participants included in each category will be calculated in terms of frequency (such as n) and proportion.

8.1.3. Binary variables

For binary variables, participants 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.

8.2. Statistical Analyses

8.2.1. Participant description

8.2.1.1. Constitution

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

8.2.1.2. Discontinuation and dropouts

Using the safety analysis set, participants completing/discontinuing this study at the end of the observation period will be summarized in terms of n and proportion. Participants discontinuing this study will be summarized by reason of discontinuation for both n and proportion. Regarding the reason of discontinuation, a list will be prepared if other is selected.

8.2.1.3. Participants excluded from analysis

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

8.2.2. Vaccinated participant characteristics and treatment history

8.2.2.1. Vaccinated participant characteristics

Using the safety analysis set, characteristics of vaccinated participants will be summarized according to Section 8.1 with respect to the following factors:

- Sex [male, female]
- Age [6 months to <2 years, 2 years to ≤4 years]
- Hepatic impairment [absent, present]
- Renal impairment [absent, present]
- Medical history [absent, present]
- Complications [absent, present]
- Past history of allergy [absent, present]

- Types of initial immunization with COVID-19 vaccines (first dose, second dose, third dose) [COMIRNATY (monovalent: Original), COMIRNATY (monovalent: XBB1.5), other]

Using the safety analysis set, a breakdown of participants 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):

- Medical history
- Complications

8.2.2.2. Status of immunization with this product

Using the safety analysis set, the status of immunization with this product will be summarized with respect to the following:

- Dose interval between the initial immunization (third dose) and the fourth vaccination (continuous) (date of 4th dose − date of 3rd dose)
- Dose interval between the initial immunization (third dose) and the fourth vaccination [<3 months (<90 days), ≥3 months]
- Vaccination site [shoulder (deltoid muscle), lateral thigh, other]
- Inoculation dose [0.2 mL, 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 will be summarized by SOC and PT in terms of n and proportion.

8.2.3.1.2. Serious adverse reactions

Serious adverse reactions will be summarized by SOC and PT in terms of n and proportion.

8.2.3.1.3. Details of adverse reactions

Adverse reactions will be summarized by SOC and PT in terms of n and proportion by each of the following factors:

- Seriousness [serious, non-serious]
- Action taken (additional treatment) [present, absent]
- Outcome [death, not resolved, resolved with sequelae, resolving, resolved/recovered, unknown]

- Severity [life-threatening, severe, moderate, mild]

Participants 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 there are both serious and non-serious events, they are regarded as serious.
- 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 participant 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: For a participant experiencing multiple adverse reactions with the same PT in different severities, the participant 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. Safety specification

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

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

  Anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock

- Myocarditis, pericarditis
  Definition: Any event corresponding to the following MedDRA SMQ (narrow):

  Noninfectious myocarditis/pericarditis

- VAED and VAERD
  Definition: Any event coded as either of the following LLTs:

  Vaccine associated enhanced respiratory disease, vaccine associated enhanced disease

  OR any event coded as one of the following PTs:

  Abdominal pain, acute hepatic failure, acute kidney injury, acute myocardial infarction, acute respiratory distress syndrome, altered state of consciousness, arrhythmia, cardiac failure, cardiogenic shock, cerebrovascular accident, chillblains, COVID-19 pneumonia, deep vein thrombosis, diarrhoea, disseminated intravascular coagulation, dyspnoea, encephalopathy, erythema multiforme, hypoxia, jaundice, meningitis, multiple organ dysfunction syndrome, multisystem inflammatory syndrome in children, myocarditis, peripheral ischaemia, pulmonary embolism, renal failure, respiratory failure, seizure, shock, tachypnoea, thrombocytopenia, vasculitis, vomiting

- Guillain-Barre syndrome
  Definition: Any event corresponding to the following MedDRA SMQ (narrow):

  Guillain-Barre syndrome

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

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

8.2.3.2. Adverse events

8.2.3.2.1. Serious adverse events

Serious adverse events will be summarized by SOC and PT in terms of n and proportion.

8.2.3.2.2. Non-serious adverse events

Non-serious adverse events will be summarized by SOC and PT in terms of n and proportion. In this tabulation, a threshold of incidence will be set as necessary, and only events with an incidence ≥ the threshold will be summarized.

8.2.3.3. Reactogenicity events

The following reactogenicity events will be summarized:

- For vaccinated participants who are younger than 2 years of age at the time of the fourth vaccination with this product
  - Local reactions: injection site tenderness, redness, and injection site swelling
  - Systemic reactions: pyrexia, decreased appetite, somnolence, and irritability
- For vaccinated participants who are 2 years or older at the time of the fourth vaccination with this product
  - Local reactions: injection site pain, redness, and injection site swelling
  - Systemic reactions: pyrexia, vomiting, diarrhoea, headache, malaise, chills, myalgia, and arthralgia

8.2.3.3.1. Local reactions

Local reactions of maximum severity (by local reaction, any local reaction) will be summarized in terms of n and proportion (by severity, any severity). Local reactions of each severity and any severity will be summarized by time of onset (Day of vaccination, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7) in terms of n and proportion, and figures corresponding to the tabulation of local reactions of each severity will be

prepared. In addition, summary statistics will be calculated by time of onset of each local reaction and any local reaction and the duration of each local reaction (date of resolution − first date of onset).

8.2.3.3.2. Systemic reactions

Systemic reactions of maximum severity (by systemic reaction, any systemic reaction) will be summarized in terms of n and proportion (by severity, any severity). Local reactions of each severity and any severity will be summarized by time of onset (Day of vaccination, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7) in terms of n and proportion, and figures corresponding to the tabulation of local reactions of each severity will be prepared. In addition, summary statistics will be calculated by time of onset of each systemic reaction and any systemic reaction and the duration of each systemic reaction (date of resolution − first date of onset).

8.2.3.3.3. Occurrence of reactogenicity events in participants excluded from the safety analysis set

Using data from CRF-collected participants, reactogenicity events reported in participants excluded from the safety analysis set will be identified and presented in a tabular form. In addition, local reactions of maximum severity (by local reaction, any local reaction) will be summarized in terms of n and proportion (by severity, any severity). Systemic reactions will be summarized in the same manner.

8.2.3.4. Information about COVID-19

Using the safety analysis set, participants underwent or not underwent any COVID-19 pathogen test (nucleic acid detection test [PCR/LAMP], antigen test) will be summarized. Among participants underwent nucleic acid detection test or antigen test, those with each result (positive or negative) will be summarized in terms of n and proportion. Furthermore, positive participants will be summarized by kind of test in terms of n and proportion, and positive participants developing COVID-19 will be summarized by n and proportion. In addition, participants with severe COVID-19 will be summarized in terms of n and proportion (denominator = the number of participants 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 the ICU
- Use of mechanical ventilation
- Use of ECMO

8.2.3.5. Subgroup analyses

Participants with at least one adverse reaction will be summarized in terms of n and proportion by each factor defined in Section 5.4.

For subgroup analyses regarding hepatic impairment and renal impairment, if judged to be necessary (Section 5.4), adverse reactions will be summarized by SOC and PT in terms of n and proportion. For reactogenicity events, local reactions of maximum severity (by local reaction, any local reaction) will be

summarized in terms of n and proportion (by severity, any severity). Systemic reactions will be summarized in the same manner.

8.2.3.6. Exploratory analyses

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

9. LISTINGS

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

- Participants included in the study
  In addition, separated lists will be presented for the following participants included in the study:
    - Participants excluded from the safety analysis set
    - Participants reported as "present" for renal impairment
    - Participants reported as "present" for hepatic impairment
    - Participants experiencing shock or anaphylaxis
    - Participants experiencing myocarditis or pericarditis
    - Participants experiencing VAED or VAERD
    - Participants experiencing Guillain-Barre syndrome
- Participants experiencing adverse reactions
- Participants experiencing serious adverse reactions
- Participants experiencing adverse events
- Participants experiencing serious adverse events
- Health observation diaries
- Health observation diaries of participants excluded from the safety analysis set
- Detailed reasons for discontinuation in participants discontinuing the study due to reasons indicated as other

In addition, documents required for application of re-examination application or J-PSUR will be prepared as appropriate.