Non-Interventional Study Protocol

C4671018

Paxlovid® PACK General Drug Use Investigation

Statistical Analysis Plan

Version: 5

Author: PPD

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TABLE OF CONTENTS

1. REVISION HISTORY

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
1 26-Apr-2022 PPD Ongoing	First edition
2 1-Dec-2022 PPD Ongoing	○ Section 2.1: Changed to refer to other documents for safety specifications. ○ Section 5.2: Description adjustment ○ Sections 5.4, 8.2.2.1, and 8.2.3.3: Added specific definitions of subgroups. ○ Section 6.3: Added handling of multiple measurements on the same day. ○ Section 7: Deleted laboratory test dates from dates used to supplement dates. ○ Section 8.2.2.1: Added age and body weight to patient characteristics, and deleted the experience of treatment with Paxlovid. ○ Section 8.2 3.1.5: Included the patients excluded from the safety analysis set in the tabulation of the occurrence of adverse reactions.
3 13-Jun-2023 PPD Ongoing	○ Section 5.2: Changed terms used in Exclusion Criterion 1 for efficacy analysis set in association with the revision of the inclusion/exclusion criteria for analysis sets and guidance for data handling to Version 3. ○ Section 5.3: Added analysis sets concerning informed consent. ○ Section 5.4: Added and deleted subgroups and provided reference levels ○ Section 6.2: Added a sensitivity analysis of hospitalization for the treatment of infection caused by SARS-CoV-2 or death from any cause. ○ Section 8.1 3: Added graphical representation of risk ratio. ○ Section 8.1.4: Adjusted the description about the number of days for time data, and added the specification for subgroup analyses. ○ Section 8.2: Added analysis sets concerning informed consent. ○ Section 8.2.2.1: Added patient characteristics and added/changed categories. ○ Section 8.2. 3.1.4: Added an analysis on the outcome of adverse reactions. ○ Section 8.2.3.2: Deleted the tabulation of all adverse events. ○ Section 8.2.3.2.1: Changed the method of tabulation of serious and non-serious adverse events. ○ Section 8.2.3.3: Specified adverse reactions to be analyzed in subgroup analyses and added estimation of risk ratio. ○ Section 8.2.4.6: Added the tabulation of patient characteristics in patients with events. ○ Section 8.2.4.7: Added risk ratio and hazard ratio estimation in subgroup analyses. ○ Section 9: Added listings. ○ Section 10.5: Added examples of tables and figures for subgroup analyses.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
4 06-Jul-2023 PPD Ongoing	○ Sections 5.4 and 8.2.4.6: Changed subgroup categories. ○ Section 8.2.2.1: Added patient characteristics and changed categories. ○ Section 8.2.3.3: Deleted statistical testing in subgroup analyses. Changed categories of factors. Added tabulation by SOC and PT for specific factors. ○ Section 8.2.4.7: Clarified the time period for subgroup analyses. ○ Section 8.2.4.8: Specified handling of measured values before the start of treatment with Paxlovid in the graphical presentation of changes over time in each subject.
5 08-Sep -2023 PPD Completed	○ Section 6.2: Adjusted the description of the definition of events in sensitivity analyses. ○ Sections 8.2.3.1.4 and 8.2.3.3: Added events to be analyzed. ○ Section 8.2.3.1.4: Added tabulation for event groups. ○ Section 8.2.4.7: Changed factors to be included in subgroup analyses ○ Section 9: Added listings.

2. INTRODUCTION

This Statistical Analysis Plan describes the statistical analysis plan of the general drug use investigation on Paxlovid® PACK (nonproprietary name, nirmatrelvir tablets and ritonavir tablets) (hereinafter referred to as this drug). In this Statistical Analysis Plan, citations from the protocol are indicated in *italics*.

2.1. Study Objectives

This study will be conducted in patients treated with this drug to understand the safety and efficacy of this drug under actual use conditions after marketing. For safety specifications, refer to the latest protocol or risk management plan.

2.2. Study Design

This is a multicenter cohort study to be conducted in patients treated with this drug. The case report form (CRF) will be filled out based on the medical records containing data obtained in usual clinical practice.

The subjects of the study are patients who have received this drug for the first time, which is a registration condition.

The observation period will be *from the start date of treatment to Day 28 after the end of treatment (the day following the end of treatment is defined as Day 1)*.

"Indications" and "dosage and administration" in the package insert (prepared in February 2022 [Version 1]) are as follows:

- Indications: Infection caused by SARS-CoV-2

- Dosage and administration: The usual dosage for adults and children aged 12 years or older with body weight of 40 kg or more is 300 mg of nirmatrelvir and 100 mg of ritonavir administered orally at the same time twice daily for 5 days.

The target sample size is *3000 patients as the safety analysis set*. *The incidence of adverse reactions to this drug in the phase 2/3 study (Study C4671005) was 7.8%. Assuming that the incidence of adverse reactions is the same in the actual use in Japan, adverse reactions will be detected in at least 214 patients with a probability of 90% with a sample size of 3000 patients. In order to detect, with a probability of 95%, at least 1 unknown adverse reaction occurring at a frequency of 0.1% or more, 3000 patients are required.*

3. INTERIM AND FINAL ANALYSES

In this study, an interim analysis will be performed *at the time of preparation of the report at 6 months after the start of the study or when the number of study patients exceeds 1000, whichever comes first*. In addition, interim analyses for periodic safety reports will be performed periodically. For an interim analysis, only necessary items selected from the full analysis items defined in this Statistical Analysis Plan will be analyzed. A final analysis will be conducted to support the application of reexamination. For the final analysis, the full items defined in this Statistical Analysis Plan will be analyzed.

4. HYPOTHESES AND DECISION RULES

Since this study is not a confirmatory study, the test will be positioned as an exploratory one.

4.1. Statistical Hypotheses

The p-value of the test result will be evaluated as descriptive statistics and the significance level will not be specified, but a threshold may be set post-hoc for the purpose of screening.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is defined as the full analysis set that is as close as possible to all patients treated with this drug. Specifically, the safety analysis set is defined as a population of registered or reported patients excluding those who meet any of the following conditions:

1. The CRF could not be collected at all (description in the report, "CRF not collected")
2. There was a violation or flaw in the contract (description in the report, "contract violation/flaw")
3. There was a violation of registration (description in the report, "violation of registration")
4. Administration of the study drug has not been reported at all (description in the report, "no information on administration")

5. Information on adverse events has not been reported at all - no visits after the first prescription day (description in the report, "no information on adverse events - no re-visits")

6. Information on adverse events has not been reported at all - there is a visit after the first prescription day but no description of information (description in the report, “no information on adverse events - no description”)

The details of each criterion are based on the latest guidance.

5.2. Efficacy Analysis Set

Efficacy Analysis Set 1 will consist of the population excluding patients who meet any of the conditions 1, 2, 3, 4, and 5 in Section 5.1 and the conditions shown below.

1. Efficacy cannot be evaluated appropriately because the condition for evaluating efficacy is not met (description in the report, "efficacy not evaluable")
   Condition: No adverse events are reported, the status of hospitalization is not reported, and both the presence or absence of worsening of severity after the start of treatment with this drug and the presence or absence of symptoms on the end date of the observation period are not reported.

2. Disease not subject to the study (description in the report, “disease not subject to the study”)
   Condition: The disease name is other than infection caused by SARS-CoV-2.

3. Inadequate treatment period or dose (description in the report, "inadequate administration")
   Condition: Nirmatrelvir has not been administered.

Efficacy Analysis Set 2 will exclude patients who meet any of the following conditions from Efficacy Analysis Set 1.

4. The patient was not an outpatient at the start of treatment with this drug (description in the report, "other than outpatient at the start of treatment")
   Condition: The patient was not an outpatient at the start of treatment with this drug.

Specific examples of identification methods for Efficacy Analysis Sets 1 and 2 are provided in Section 10.1 Table 1.

Efficacy Analysis Set 3 will exclude patients who meet the following conditions from Efficacy Analysis Set 2.

5. No risk factors for aggravation at the start of treatment with this drug (description in the report, "no risk factors for aggravation")
   Condition: The patient does not meet any of the following risk factors for aggravation. If the age is unknown, it will be considered that the condition for risk factors for aggravation is not met. Similarly, when BMI cannot be calculated, smoking status is unknown or not provided, and medical history is unknown or not provided, it will be considered that each condition is not satisfied.

   - ≥60 years of age

- BMI > 25 kg/m^2
- Smoking status "present" (a rough guide for "present": current smoking at the start of treatment with this drug [smoking within 30 days] and having smoked at least 100 cigarettes in their lifetime)
- At least one of the diseases and syndromes recorded as medical history that is "ongoing" and “corresponds to risk factor for aggravation of infection caused by SARS-CoV-2"

The subgroup analyses in Efficacy Analysis Set 3 will be defined for populations similar to the mITT and mITT1, which were the primary analysis sets for efficacy evaluation in Study C4671005 (Section 5.4).

5.3. Other Analysis Sets

5.3.1. Consented Safety Analysis Set

Analysis set limited to patients who gave consent among the safety analysis set

5.3.2. Consented Efficacy Analysis Set

Analysis set limited to patients who gave consent among the efficacy analysis sets

5.4. Subgroups

Subgroup analyses of safety will be performed for the following patient characteristics. Descriptions in brackets indicate the levels of subgroups, and the underlined level indicates the standard level for calculation of risk ratio.

- Hepatic impairment [absent, present, unknown]
- Hepatic impairment [absent, mild, moderate, severe, unknown (presence unknown or severity unknown)]
- Renal impairment [absent, present, unknown]
- Renal impairment [absent, mild, moderate, severe, unknown (presence unknown or severity unknown)]
- Age [<15 years, ≥15 years]
- Age [≤65 years, ≥65 years]
- Age [<18 years, ≥18 years]
- Age [≤65 years, ≥65 to <75 years, ≥75 years]
- Pregnancy [absent, present] * Female only

Subgroup analyses of safety will be performed for the following other factors:

- Contraindications for coadministration/precautions for coadministration [both absent, precautions for coadministration present, contraindications for coadministration present] Patients with precautions for coadministration and patients with contraindications for coadministration may overlap. For patients with precautions for coadministration and patients with contraindications for coadministration, events after the start of coadministration will be included.

- Complicated with HIV infection and concomitantly using anti-HIV therapy including ritonavir or cobicistat [absent, present] * Specifically, patients concomitantly using ritonavir or cobicistat will be classified as present and other patients as absent.

Patients possibly contraindicated in the package insert of this drug (hereinafter referred to as contraindicated patients) will be extracted based on separately specified criteria and subgroup analysis of safety will be performed.

Subgroup analyses of efficacy will be performed for the following patient characteristics. Unless otherwise specified, analysis will be performed for Efficacy Analysis Sets 1 and 3. Descriptions in brackets indicate the levels of subgroups, and the underlined level indicates the standard level for calculation of risk ratio and hazard ratio.

- Combination of admission status at the start of treatment with this drug [inpatient, outpatient] and risk factors for aggravation [risk factors present, risk factors absent, risk factors unknown]. To be performed in Efficacy Analysis Set 1.

- History of use of drugs for the treatment of infection caused by SARS-CoV-2 [history of use absent, history of use present, unknown]

- Number of days from the onset of symptoms of infection caused by SARS-CoV-2 to the start of treatment with this drug [within 3 days, 4 or 5 days, 6 days or more, unknown] If the onset of symptoms and the start of treatment with this drug are on the same day, the number of days will be 0.

- Symptoms and severity of infection caused by SARS-CoV-2 at the start of treatment with this drug [no symptoms, mild, moderate I, moderate II, severe, symptoms or severity unknown]

- Number of risk factors for aggravation of infection caused by SARS-CoV-2 [none, 1, 2, 3, 4, number unknown, unknown]. If there are risk factors but the number is unknown, the patient will be classified as "number unknown." If it is not known that there are risk factors, the patient will be classified as “unknown.”

- SARS-CoV-2 vaccination history [present, absent, unknown]

- Number of SARS-CoV-2 vaccination doses (vaccination on or before the day before the start of treatment with this drug) [none, 1, 2, 3, 4 or more, unknown]

- Hepatic impairment [absent, present, unknown]

- Hepatic impairment [absent, mild, moderate, severe, unknown (presence unknown or severity unknown)]
- Renal impairment [absent, present, unknown]
- Renal impairment [absent, mild, moderate, severe, unknown (presence unknown or severity unknown)]
- Age [<15 years, ≥15 years]
- Age [≤65 years, ≥65 years]
- Pregnancy [absent, present] * Female only

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

The safety evaluation period is defined as the observation period in Section 2.2. The number of days from the start date of treatment to the onset date of event will be calculated as [event onset date – start date of treatment with this drug + 1].

- Adverse reactions: Adverse events for which the causal relationship was considered as related by the treating physician
- Adverse events: All-causality adverse events
- Serious adverse events or serious adverse reactions: Adverse events or adverse reactions considered by the treating physician to be serious
- Events to be handled as safety specifications are specified separately.

6.2. Efficacy Endpoints

Unless otherwise specified, the efficacy evaluation period will be the observation period in Section 2.2. The number of days from the start date of treatment to the onset date of event will be calculated as [event onset date – start date of treatment with this drug + 1]. In the analyses related to the end date of the observation period, the primary definition of the end date will be up to Day 28 after the end of treatment, and the secondary definition will also be defined for evaluation (Section 10.2 Table 2).

The following efficacy endpoints are defined for Efficacy Analysis Sets 1, 2, and 3.

- Worsening of severity of infection caused by SARS-CoV-2: Whether the severity of infection caused by SARS-CoV-2 has worsened will be evaluated. However, when the severity is severe at the start of this drug and does not worsen during the observation period, it will be considered as "severe at the start of treatment." Otherwise, if the date of the highest severity is the day after the end of the evaluation period or later, it will be handled as "unknown (highest severity recorded after the end of evaluation period)." Therefore, the categories will be as follows. “Worsened” will be considered as an

event. The expected entries in the CRF and their handling, and assessment of endpoints are shown in Section 10.3 Table 3.

  - Not worsened, worsened, severe at the start of treatment, unknown (highest severity recorded after the end of the evaluation period, worsening unknown, no record of worsening)

- Highest severity: The highest severity will be evaluated for patients with the above worsening of severity of infection caused by SARS-CoV-2. If the highest severity is unknown but the severity is considered to have worsened, the highest severity will be "moderate II or severe (indistinguishable)" for patients with the initial severity of moderate I and as "severe" for patients with the initial severity of moderate II. It consists of the following categories. The expected entries in the CRF and their handling, and assessment of endpoints are shown in Section 10.3 Table 3.

  - Mild, moderate I, moderate II, severe, moderate II or severe (indistinguishable), unknown (severity unknown, severity not recorded)

- Highest severity (moderate II or severe): For patients with the above worsening of severity of infection caused by SARS-CoV-2, the highest severity of moderate II, severe, and moderate II or severe (indistinguishable) will be defined as "moderate II or severe" and evaluated as an event. If the highest severity is unknown but the severity is considered to have worsened, the highest severity will be "moderate II or severe (indistinguishable)" and "severe" for patients with the initial severity of moderate I and moderate II, respectively, and the patient will be considered to have experienced an event.

- Presence/absence and severity of symptoms as of the end date of the observation period: It consists of the following categories:

  - No symptoms, symptoms present (mild, moderate I, moderate II, severe, severity unknown), unknown (symptoms unknown, symptoms not recorded)

- Resolution of symptoms from the start of treatment with this drug as of the end date of the observation period: The absence of symptoms on the end date of the observation period in patients with symptoms at the start of treatment with this drug will be considered as resolution of symptoms and evaluated. If the patient has no symptoms at the start of treatment with this drug, the patient will be considered to have no symptoms at the start of treatment. It consists of the following categories. The expected entries in the CRF and their handling, and assessment of endpoints are shown in Section 10.3 Table 4.

  - Resolved, not resolved, no symptoms at the start of treatment, unknown (resolution unknown, symptoms not recorded)

- Improvement in severity from the start of treatment with this drug as of the end date of the observation period: The improvement in severity from the start of treatment with this drug on the end date of the observation period will be evaluated. It consists of the following categories. The expected entries in the CRF, their handling, and assessment of endpoints are shown in Section 10.3 Table 5.

  - Improved, not improved, no symptoms at the start of treatment, unknown (improvement unknown, severity not recorded)

- Resolution of symptoms after worsening of severity during the observation period as of the end date of the observation period: For patients with worsening of severity during the observation period, the absence of symptoms on the end date of the observation period will be considered as resolution of symptoms and evaluated. It consists of the following categories. Even if the end date of the observation period and the date of the highest severity are the same, the patient will be included in the analysis.

  - Resolved, not resolved, unknown (resolution unknown, symptoms not recorded)

- Improvement in severity after worsening of severity during the observation period as of the end date of the observation period: For patients with worsening of severity during the observation period, improvement from the highest severity on the end date of the observation period will be evaluated. It consists of the following categories. Even if the end date of the observation period and the date of the highest severity are the same, the patient will be included in the analysis.

  - Improved, not improved, unknown (improvement unknown, severity not recorded)

- Death from any cause: Death reported by Day 28 after the end of treatment will be considered as an event and evaluated. Death should be confirmed with the outcome information of adverse events. Unknown if no adverse event is reported (Section 10.1 Table 1).
  The number of days from the start date of treatment to the onset date of event will be calculated. If an event including the case of unknown has not occurred, the patient will be censored at the date of the last observation or Day 28 after the end of treatment, whichever is earlier.

The following efficacy endpoint is defined in Efficacy Analysis Sets 2 and 3.

- Hospitalization for the treatment of infection due to SARS-CoV-2 or death from any cause: Hospitalization for treatment of infection caused by SARS-CoV-2 or death reported by Day 28 after the end of treatment will be considered as an event and evaluated. Death should be confirmed with the outcome information of adverse events. Unknown if neither the status of hospitalization nor the presence or absence of adverse events is reported. When only the status of hospitalization or the presence or absence of adverse events is reported and hospitalization or death applicable to an event is observed, it will be considered as an event, and other cases will be regarded as unknown (Section 10.1 Table 1). In addition, each event of hospitalization and death will be evaluated.
  The number of days from the start date of treatment to the onset date of event will be calculated, but the onset date of event will be the earlier date of hospitalization or death. Even if only either the status of hospitalization or the presence or absence of adverse events is reported, the date of hospitalization or death will be regarded as the onset date of event if hospitalization or death applicable to an event is confirmed. If the status of hospitalization is not reported and death is observed, it is acceptable to consider the date of death as the onset date of event because the status of hospitalization is unknown, although it may overestimate the time to event. If no event has occurred, the patient will be censored at the date of the last observation or Day 28 after the end of treatment, whichever is earlier. Even in

the case of unknown, the patient will be censored at the start date of treatment if neither the status of hospitalization nor the presence or absence of adverse events is reported and if the status of hospitalization is not reported and the patient has not died, or at the date of last observation or Day 28 after the end of treatment, whichever is earlier, if the presence or absence of adverse events is not reported and the patient has not been hospitalized.

- For the purposes of sensitivity analysis, hospitalization for the treatment of infection caused by SARS-CoV-2 is defined as follows. For hospitalizations not meeting this, the patient will be censored according to the above definition.

    - There are concomitant medications for infection caused by SARS-CoV-2 or concomitant non-drug therapies due to infection caused by SARS-CoV-2 on or after the date of admission.
      Concomitant medications for infection caused by SARS-CoV-2 are as follows: remdesivir (Veklury), molnupiravir (Lagevrio), dexamethasone, baricitinib (Olumiant), casirivimab/imdevimab (Ronapreve), sotrovimab (Xevudy), tocilizumab (Actemra), tixagevimab/cilgavimab (Evusheld), and ensitrelvir fumarate (Xocova). * Categories will be set appropriately for drugs for the treatment of infection caused by SARS-CoV-2 in addition to the drugs listed.

6.3. Other Endpoints

- Viral load

- Body temperature: If more than one measurement is taken on the same day regardless of before or after the start of treatment with this drug, the higher value will be used for the analysis.

- Percutaneous arterial oxygen saturation (SpO_2): If more than one measurement is taken on the same day regardless of before or after the start of treatment with this drug, the lower value will be used for the analysis.

6.4. Covariates

In Study C4671005, subgroup analyses of COVID-19-related hospitalization or death (all causes) reported up to Day 28, an efficacy endpoint, were performed for age, sex, race, BMI, serology, viral load, comorbidities, and number of comorbidities. The results were consistent with those in the whole mITT population in many subgroups and the incidence was significantly or more decreased in the subgroups with a large number of subjects or with a high incidence (Study C4671005, Interim Clinical Study Report). These will not be used as covariates in this study.

While the impact of viral variants and SARS-CoV-2 vaccination history on efficacy has not been evaluated in clinical studies, they are potential covariates.

Since HIV-infected patients may concomitantly use anti-HIV therapy including ritonavir with this drug, this is a potential covariate for the safety of this drug.

7. HANDLING OF MISSING DATA

If the seriousness, causal relationship, treatment, and outcome of an adverse event are missing, the data will be handled as "unknown" for tabulation.

If there are no measured values within the acceptable window for each time point of evaluation of efficacy endpoints (Appendix 2), the values will be handled as missing and will not be imputed. Definitions of acceptable windows for other endpoints are provided in Appendix 2.

If the date of admission is missing or partial, the last complete date among the following will be used as the imputed date.

- Start date of this drug
- The first day of the month of the same month as the date of admission (if the day of admission is missing and the month and year are available)
- The first day of the year of the same year as the date of admission (if the month and day of admission are missing and the year is available)

If the date of death and the date of last observation are missing or partial, the latest complete date among the following will be used as the imputed date.

- Start date/end date of this drug
- Start date/end date of concomitant drug therapy
- Start date/end date of concomitant non-drug therapy
- Viral test
- Date of measurement of body temperature/SpO_2
- Date of admission/date of discharge
- Date of efficacy evaluation (date of the highest severity/date of evaluation at the end of the observation period)
- Date of onset of adverse event, resolution/recovery of adverse event, date of death
- The first day of the month of the same month as the date of last observation (if the day of last observation is missing and the month and year are available)
- The first day of the year of the same year as the date of last observation (if the month and day of last observation are missing and the year is available)

The policy for handling uncleaned data is described below.

- Items of missing data: Values will be handled as missing (category of categorical variables is "not recorded") in both tabulation and listing.

- Items of inconsistent data: Inconsistent data will be handled as missing in both tabulation and listing. However, a list of data handling will be prepared separately.

- No signature: The descriptions in the CRF without the signature of the contract physician (including the case of only the signature of a physician other than the contract physician) will be handled as missing in both tabulation and listing.

8. STATISTICAL METHODS AND ANALYSES

8.1. Statistical Methods

8.1.1. Continuous variables

For continuous variables, summary statistics (n, mean, standard deviation, median, 1st quartile, 3rd quartile, maximum, and minimum) will be calculated.

8.1.2. Categorical variables

For categorical variables, patients falling into each category will be summarized in terms of frequency and proportion.

8.1.3. Binary variables

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

When a comparison for proportion is made between subgroups, the risk ratio and its 95% confidence interval will be calculated. In addition, the risk ratio and its 95% confidence interval will be graphically presented.

If a test is performed, Fisher's exact test will be used for the relationship with nominal scale data and Cochran-Armitage test (exact method) for the relationship with ordinal scale data. However, if it is difficult to perform the exact method, a chi-square test or Cochran-Armitage test with normal approximation will be used as an alternative to the exact method.

8.1.4. Time (to event) data

Kaplan-Meier's method will be used to determine the median, 1st quartile, and 3rd quartile. The time point incidence will be calculated on Days 3, 5, 7, 14, 21, and 28 after the start of treatment with this drug (the start date of treatment will be defined as Day 1). Confidence intervals will be estimated using the log-log transformation (corresponding to specifying a loglog under the conftype option in the proc lifetest statement of the SAS®, lifetest procedure). In addition, Kaplan-Meier plots will be prepared.

When time data are compared between subgroups, the hazard ratio of events and its 95% confidence interval will be calculated using Cox proportional hazard model (Breslow method for handling ties). In addition, the hazard ratio and 95% confidence interval will be graphically presented.

8.2. Statistical Analyses

Analyses in the safety analysis set and the efficacy analysis set will also be performed in the consented safety analysis set and the consented efficacy analysis set, but the details will be separately specified. At the time of analysis, the safety analysis set and the efficacy analysis set will be replaced with the consented safety analysis set and the consented efficacy analysis set, respectively.

8.2.1. Description of patients

8.2.1.1. Constitution

The numbers of patients who completed the study, patients included in safety analysis, patients included in efficacy analysis 1, patients included in efficacy analysis 2, and patients included in efficacy analysis 3 will be determined. In addition, CRF-uncollected patients, patients excluded from safety analysis, patients excluded from efficacy analysis 1, patients excluded from efficacy analysis 2, and patients excluded from efficacy analysis 3 will be counted as a total and by reason for exclusion.

8.2.1.2. Discontinuation

In the safety analysis set, Efficacy Analysis Set 1, Efficacy Analysis Set 2, and Efficacy Analysis Set 3, the number and proportion of patients who discontinued the study will be summarized by timing (during treatment, within 7 days after the end of treatment, within 14 days after the end of treatment, within 21 days after the end of treatment, and within 28 days after the end of treatment). The same summarization will also be performed by reason of discontinuation. The number and proportion of completed patients will be summarized.

8.2.1.3. Patients excluded from analysis

Patients excluded from safety analysis, patients excluded from efficacy analysis 1, patients excluded from efficacy analysis 2, and patients excluded from efficacy analysis 3 will be listed in tabular form with their reason for exclusion.

8.2.2. Patient characteristics and treatment history

8.2.2.1. Patient characteristics

In the safety analysis set, Efficacy Analysis Set 1, Efficacy Analysis Set 2, and Efficacy Analysis Set 3, the following patient characteristics will be summarized in accordance with Section 8.1:

- Sex [male, female]
- Age (continuous)
- Age [<15 years, ≥15 years]
- Age [<65 years, ≥65 years]
- Age [<18 years, ≥18 years]
- Age [<65 years, ≥65 to <75 years, ≥75 years]
- Age [≥60 years] * ≥60 years is a risk factor for aggravation.
- Age and body weight [≥12 to <18 years and ≥40 kg, ≥6 to <12 years and ≥40 kg, ≥6 to <18 years and ≥20 to <40 kg, ≥6 to <18 years and <20 kg, ≥2 to <6 years, <2 years]

- Pregnancy [absent, present] * Female only
- Inpatient/outpatient status at the start of treatment with this drug [outpatient, inpatient]
- Reason for hospitalization at the start of treatment with this drug [treatment of infection caused by SARS-CoV-2, isolation, other]
- BMI [≤25 kg/m^2, >25 kg/m^2, unknown] * ≥25 kg/m^2 is a risk factor for aggravation.
- Smoking status [no, smoked in the past, smoking, unknown] * "Smoking" is a risk factor for aggravation.
- Disease subject to the study [infection caused by SARS-CoV-2, other]
- Symptoms of infection caused by SARS-CoV-2 [present, absent, unknown]
- Number of days from the onset of symptoms of infection caused by SARS-CoV-2 to the start of treatment with this drug [within 3 days, 4 or 5 days, 6 days or more, unknown] (If the onset of symptoms and the start of treatment with this drug are observed on the same day, the number of days will be 0.)
- Severity of symptoms of infection caused by SARS-CoV-2 [mild, moderate I, moderate II, severe, unknown]
- Hepatic impairment [absent, present, unknown] [if present: mild, moderate, severe, unknown]
- Renal impairment [absent, present, unknown] [if present: mild, moderate, severe, unknown]
- Medical history [absent, present]
- History of infection caused by SARS-CoV-2 [absent, present]
- Complications [absent, present]
- Complications corresponding to risk factors for aggravation of infection caused by SARS-CoV-2 [absent, present] * "Present" is a risk factor for aggravation.
- Risk factors for aggravation of infection caused by SARS-CoV-2 [absent, present, unknown] [if present: 1, 2, 3, 4, number unknown] * If the number of applicable risk factors is unknown, "number unknown" should be selected. If it is not known that there are risk factors, the patient will be classified as “unknown.”
- Complicated with HIV infection and concomitantly using anti-HIV therapy including ritonavir or cobicistat [absent, present] * Specifically, patients concomitantly using ritonavir or cobicistat will be classified as present and other patients as absent.
- Prior medications for infection caused by SARS-CoV-2 [absent, present, unknown]

- Breakdown of prior medications for infection caused by SARS-CoV-2 [remdesivir (Veklury), molnupiravir (Lagevrio), dexamethasone, baricitinib (Olumiant), casirivimab/imdevimab (Ronapreve), sotrovimab (Xevudy), tocilizumab (Actemra), tixagevimab/cilgavimab (Evusheld), ensitrelvir fumarate (Xocova), other] * Categories will be set appropriately for drugs for the treatment of infection caused by SARS-CoV-2 in addition to the drugs listed.

- Prior medications for infection caused by SARS-CoV-2 (continued at the start of treatment with this drug) [absent, present, unknown]

- Breakdown of prior medications for infection caused by SARS-CoV-2 (continued at the start of treatment with this drug) [remdesivir (Veklury), molnupiravir (Lagevrio), dexamethasone, baricitinib (Olumiant), casirivimab/imdevimab (Ronapreve), sotrovimab (Xevudy), tocilizumab (Actemra), tixagevimab/cilgavimab (Evusheld), ensitrelvir fumarate (Xocova), other] * Categories will be set appropriately for drugs for the treatment of infection caused by SARS-CoV-2 in addition to the drugs listed.

- SARS-CoV-2 vaccination history (vaccination on or before the day before the start of treatment with this drug) [absent, present, unknown]

- Breakdown of SARS-CoV-2 vaccination history (vaccination on or before the day before the start of treatment with this drug) [Comirnaty, Spikevax, Vaxzevria, other, unknown]

- Number of SARS-CoV-2 vaccination doses (vaccination on or before the day before the start of treatment with this drug) [absent, present, unknown] [if present: 1, 2, 3, 4 or more]

- SARS-CoV-2 viral test before the start of treatment with this drug (including the start date of treatment) [present, absent]

- Results of SARS-CoV-2 viral test before the start of treatment with this drug (including the start date of treatment) [positive, negative]

- SARS-CoV-2 viral load (continuous) before the start of treatment with this drug (including the start date of treatment)

- SARS-CoV-2 viral load before the start of treatment with this drug (including the start date of treatment) [≥ 4 $\log_{10}$ copies/mL, <4 $\log_{10}$ copies/mL, unknown] [≥ 7 $\log_{10}$ copies/mL, <7 $\log_{10}$ copies/mL, unknown]

- SARS-CoV-2 variant before the start of treatment with this drug (including the start date of treatment) (wild strain, Beta variant, Gamma variant, Delta variant, Omicron variant, unknown)

- Percutaneous arterial oxygen saturation (SpO_2) before the start of treatment with this drug (including the start date of treatment) [$\geq 96\%$, $>93\%$ to $<96\%$, $\leq 93\%$, unknown]

- Percutaneous arterial oxygen saturation (SpO_2) before the start of treatment with this drug (including the start date of treatment) [$\geq 95\%$, $<95\%$, unknown]

- Findings of pneumonia due to infection caused by SARS-CoV-2 at the start of treatment with this drug [absent, present, unknown]
- Administration of oxygen for infection caused by SARS-CoV-2 performed since before the start of treatment with this drug [present]
- Artificial ventilation with intubation for infection caused by SARS-CoV-2 performed since before the start of treatment with this drug [present]
- ECMO for infection caused by SARS-CoV-2 performed since before the start of treatment with this drug [present]

Using the safety analysis set, the following aspects of patients will be summarized in terms of number and proportion by system organ class (SOC) and by preferred term (PT):

- Breakdown of medical history
- Breakdown of complications
- Breakdown of complications (those corresponding to risk factors for aggravation of infection caused by SARS-CoV-2)

In the safety analysis set, Efficacy Analysis Set 1, Efficacy Analysis Set 2, and Efficacy Analysis Set 3, the following number and proportion of patients will be tabulated. All the therapies used between the start date of treatment with this drug and Day 28 after the end of treatment will be included.

- Breakdown of concomitant drug therapies (those other than SARS-CoV-2 vaccines whose reason for use is infection caused by SARS-CoV-2) [remdesivir (Veklury), molnupiravir (Lagevrio), dexamethasone, baricitinib (Olumiant), casirivimab/imdevimab (Ronapreve), sotrovimab (Xevudy), tocilizumab (Actemra), tixagevimab/cilgavimab (Evusheld), ensitrelvir fumarate (Xocova), other]
  * Categories will be set appropriately for drugs for the treatment of infection caused by SARS-CoV-2 in addition to the drugs listed.
- Breakdown of other concomitant drug therapies (those other than SARS-CoV-2 vaccines whose reason for use is infection caused by SARS-CoV-2)
- Breakdown of concomitant drug therapies (those other than SARS-CoV-2 vaccines whose reason for use is other than infection caused by SARS-CoV-2)
- Breakdown of concomitant drug therapies (SARS-CoV-2 vaccines)
- Breakdown of concomitant non-drug therapies (those whose reason for use is infection caused by SARS-CoV-2)
- Breakdown of concomitant non-drug therapies (those whose reason for use is adverse events)

8.2.2.2. Exposure of this drug

Using the safety analysis set, exposure of this drug will be summarized with respect to the following aspects:

- Duration of treatment [1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or more]: The number of days from the date of first dose to the date of last dose in this study, including non-dosing periods.
- Number of days of treatment [1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or more]: The number of days this drug is actually administered in this study.
- Dose per administration (nirmatrelvir/ritonavir) [only 300 mg/100 mg, other than 300 mg/100 mg present (150 mg/100 mg present, other doses present)] [Breakdown of other]: Descriptions in parentheses indicate the breakdown of "other than 300 mg/100 mg present" and patients may overlap.

The duration of treatment is defined as the number of days from the date of first dose to the date of last dose in this study, including non-dosing periods. The number of days of treatment is defined as the number of days this drug is actually administered.

8.2.3. Safety analysis

Refer to Section 6.1 for the evaluation period for adverse reactions and adverse events. The listing will include all 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 number and proportion.

8.2.3.1.2. Serious adverse reactions

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

8.2.3.1.3. Details of adverse reactions

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

- Seriousness [serious, non-serious]
- Known/unknown [known, unknown]
- Action taken [permanent discontinuation, temporary discontinuation or dose reduction]
- Outcome [fatal, not recovered, recovered with sequelae, improved, resolved/recovered, unknown]
- Outcome [fatal]

Multiple adverse reactions of the same PT occurring in the same patient will be handled as follows:

- Seriousness: If both serious and non-serious reactions of the same PT occurred in the same patient, the patient will be counted as one with serious reaction.
- Known/unknown: If both known and unknown reactions of the same PT occurred in the same patient, the patient will be counted as one with unknown reaction.
- Action taken: If multiple actions were taken for adverse reactions of the same PT, only one category of action will be adopted with "permanent discontinuation," "temporary discontinuation or dose reduction," and "dose increase or no change" being given priority in this order.
- Outcome: The outcome for the last event will be adopted.

8.2.3.1.4. Outcome of adverse reactions

For events with PTs of dysgeusia, taste disorder, diarrhoea, vomiting, nausea, decreased appetite, and rash, summary statistics of the time (days) from the start date of treatment with this drug to the onset date of the initial adverse reaction and the time (days) from the onset date of the initial adverse reaction to the date of resolution/recovery will be calculated in accordance with Section 8.1.1. The number of patients without resolution or recovery will be presented.

In addition, summary statistics will be tabulated for each of the above 7 events of PTs, other events, and all events according to the following definitions in accordance with Section 8.1.1.

- Time (days) from the start date of treatment with this drug to the onset date of the adverse reaction that occurred first among the initial events within each PT
- Time (days) from the onset date to the date of resolution/recovery of the adverse reaction with the longest time among the initial events within each PT: If the initial event did not resolve or recover in any PT, the patient will not be included in this tabulation and will be presented in the number of patients without resolution or recovery.

8.2.3.1.5. Safety specifications

For the following safety specifications, patients who experienced relevant events will be summarized in terms of number and proportion:

- Toxic epidermal necrolysis/oculomucocutaneous syndrome
- Hepatic impairment
- Hyperglycemia/diabetes mellitus
- Bleeding tendency

In addition, patients who experienced each safety specification will be summarized by action taken and outcome for each SOC and PT.

8.2.3.1.6. Adverse reactions in patients excluded from the safety analysis set

Among CRF-collected patients, a listing of adverse reactions will be prepared for patients excluded from the safety analysis set. In addition, patients with an adverse reaction will be summarized by SOC and PT.

8.2.3.2. Adverse events

8.2.3.2.1. Adverse events by serious/non-serious

The number and proportion of patients with serious adverse events will be summarized by SOC and PT. Non-serious adverse events will also be tabulated in the same manner, but the threshold for the incidence will be set as necessary, and only events with the incidence at or above the threshold will be tabulated. This analysis will be performed only for the consented safety analysis set.

8.2.3.3. Subgroup analyses

The number and proportion of patients who experienced at least 1 adverse reaction will be tabulated by factor specified in Section 5.4. In addition, risk ratios of the incidence of adverse reactions between subgroups will be calculated as described in Section 8.1.3. However, if there is a category with less than 10 patients and it is determined difficult after reconsideration of the classification of categories, the risk ratio for the category will not be calculated. Similar analyses will be performed for adverse reactions with PTs of dysgeusia, taste disorder, diarrhoea, vomiting, nausea, decreased appetite, and rash by each of the following factors.

Descriptions in brackets indicate the levels of subgroups, and the underlined level indicates the standard level for calculation of risk ratio.

- Hepatic impairment [absent, present, unknown]
- Hepatic impairment [absent, mild, moderate, severe, unknown (presence unknown or severity unknown)]
- Renal impairment [absent, present, unknown]
- Renal impairment [absent, mild, moderate, severe, unknown (presence unknown or severity unknown)]
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Age [<18 years, ≥18 years]
- Age [<65 years, ≥65 to <75 years, ≥75 years]
- Pregnancy [absent, present] * Female only
- Contraindications for coadministration/precautions for coadministration [both absent, precautions for coadministration present, contraindications for coadministration present] Patients with precautions for coadministration and patients with contraindications for coadministration may overlap. For patients

with precautions for coadministration and patients with contraindications for coadministration, events after the start of coadministration will be included.

- Complicated with HIV infection and concomitantly using anti-HIV therapy including ritonavir or cobicistat [absent, present] * Specifically, patients concomitantly using ritonavir or cobicistat will be classified as present and other patients as absent.

Adverse reactions will be summarized in terms of number and proportion by each of the following factors among the factors specified in Section 5.4 for each SOC and PT.

- Hepatic impairment [absent, present]
- Hepatic impairment [absent, mild, moderate, severe]
- Renal impairment [absent, present]
- Renal impairment [absent, mild, moderate, severe]
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Age [<18 years, ≥18 years]
- Age [<65 years, ≥65 to <75 years, ≥75 years]
- Pregnancy [absent, present] * Female only
- Contraindications for coadministration/precautions for coadministration [both absent, precautions for coadministration present, contraindications for coadministration present] Patients with precautions for coadministration and patients with contraindications for coadministration may overlap. For patients with precautions for coadministration and patients with contraindications for coadministration, events after the start of coadministration will be included.
- Complicated with HIV infection and concomitantly using anti-HIV therapy including ritonavir or cobicistat [absent, present] * Specifically, patients concomitantly using ritonavir or cobicistat will be classified as present and other patients as absent.

A listing of adverse reactions will be prepared for contraindicated patients.

8.2.3.4. Exploratory analyses

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

8.2.4. Efficacy analyses

Refer to Section 6.2 for the efficacy evaluation period. Sensitivity analysis will be performed by changing the evaluation period based on the end date of the observation period to the secondary definition described in Section 6.2 but not for subgroup analyses and exploratory analyses.

8.2.4.1. Worsening of severity and highest severity of infection caused by SARS-CoV-2

The following analyses will be performed in Efficacy Analysis Sets 1, 2, and 3.

For worsening of severity of infection caused by SARS-CoV-2, the frequency and proportion of each category will be calculated. The confidence interval of the proportion will also be calculated for "worsened."

For the highest severity, the frequency and proportion of each category will be calculated. The denominator of the proportion will be the number of patients with worsening. For the highest severity (moderate II or severe), the frequency and proportion of moderate II or severe and its breakdown (moderate II, severe, moderate II or severe [indistinguishable]), and the confidence interval will be calculated.

8.2.4.2. Presence or absence and severity of symptoms as of the end date of the observation period

In Efficacy Analysis Sets 1, 2, and 3, the frequency and proportion of each category will be calculated. The breakdown of "symptoms present" will also be tabulated.

8.2.4.3. Resolution of symptoms and improvement in severity from the start of treatment with this drug as of the end date of the observation period

The following analyses will be performed in Efficacy Analysis Sets 1, 2, and 3.

For resolution of symptoms from the start of treatment with this drug as of the end date of the observation period, the frequency and proportion of each category will be calculated. For "resolved," the confidence interval of the proportion will also be calculated.

For the improvement in severity from the start of treatment with this drug as of the end date of the observation period, the frequency and proportion of each category will be calculated. For "improved," the confidence interval of the proportion will also be calculated.

8.2.4.4. Resolution of symptoms and improvement in severity after worsening of severity during the observation period as of the end date of the observation period

Among the patients in Efficacy Analysis Sets 1, 2, and 3, the following analyses will be performed in those who showed worsening of the severity of infection caused by SARS-CoV-2 after the start of treatment with this drug (patients with worsening).

The frequency and proportion of each category will be calculated for resolution of symptoms after worsening of severity during the observation period as of the end date of the observation period. For "resolved," the confidence interval of the proportion will also be calculated.

For the improvement in severity after worsening during the observation period as of the end date of the observation period, the frequency and proportion of each category will be calculated. For "improved," the confidence interval of the proportion will also be calculated.

8.2.4.5. Death from any cause

Deaths from any cause will be analyzed in Efficacy Analysis Sets 1, 2, and 3 as described in Section 8.1.4.

The frequency and proportion of events and censoring will be calculated separately. The period at risk of events is defined as the number of days from the start date of treatment to the onset date of event, date of last observation, or Day 28 after the end of treatment, whichever comes first, and the mean will be calculated.

For the number of days from the start date of treatment to the onset date of event, frequency and its proportion will be calculated and shown in a figure.

8.2.4.6. Hospitalization for treatment of infection caused by SARS-CoV-2 or death from any cause

Hospitalization for treatment of infection caused by SARS-CoV-2 or death from any cause will be analyzed in Efficacy Analysis Sets 2 and 3 in accordance with Section 8.1.4.

The frequency and proportion of events and censoring will be calculated separately. Events will be tabulated not only for hospitalization or death but also for each. The period at risk of events is defined as the number of days from the start date of treatment to the onset date of event, date of last observation, or Day 28 after the end of treatment, whichever comes first, and the mean will be calculated.

For the number of days from the start date of treatment to the onset date of event, frequency and its proportion will be calculated and shown in a figure.

For patients who developed events, the following patient characteristics will be tabulated according to Section 8.1.

- Age
- Number of risk factors for aggravation of infection caused by SARS-CoV-2 [absent, 1, 2, 3, 4, number unknown, unknown] * If the number of applicable risk factors is unknown, "number unknown" should be selected. If it is not known that there are risk factors, the patient will be classified as “unknown.”
- Number of SARS-CoV-2 vaccination doses (vaccination on or before the day before the start of administration of this drug) [none, 1, 2, 3, 4 or more, unknown]

As a sensitivity analysis, the above analysis will be performed by changing the definition to the event definition of hospitalization shown in Section 6.2.

8.2.4.7. Subgroup analyses

Subgroup analyses of the following efficacy endpoints will be performed based on Section 8.1 by factor specified in Section 5.4. However, if there is a category with less than 10 patients and it is determined difficult after reconsideration of the classification of categories, the ratio for the category will not be calculated. The analysis sets to be analyzed are specified in Section 5.4.

- Worsening of severity: The risk ratio of “worsened” and the 95% confidence interval will be estimated.
- Resolution of symptoms: The risk ratio of “resolved” and the 95% confidence interval will be estimated (only for the entire period). * Excluding the factor "symptoms and severity of infection caused by SARS-CoV-2 at the start of treatment with this drug"
- Improvement in severity: The risk ratio of “improved” and the 95% confidence interval will be estimated (only for the entire period). * Excluding the factor "symptoms and severity of infection caused by SARS-CoV-2 at the start of treatment with this drug"
- Death from any cause: The hazard ratio of events from the start of treatment with this drug to Day 28 and the 95% confidence interval will be estimated.
- Hospitalization or death from any cause: The hazard ratio of events from the start of treatment with this drug to Day 28 and the 95% confidence interval will be estimated.
- Hospitalization or death from any cause (sensitivity analysis): The hazard ratio of events from the start of treatment with this drug to Day 28 and the 95% confidence interval will be estimated.

8.2.4.8. Exploratory analyses

For Efficacy Analysis Set 1, changes over time in viral load, body temperature, and percutaneous arterial oxygen saturation (SpO_2) in individual patients will be superimposed on the figures. For measured values before the start of treatment with this drug (including the start date of treatment), the last measured value before the start of treatment with this drug will be shown based on the handling of each endpoint in Section 6.3.

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

9. LISTINGS

The following listings will be prepared:

- Patient listing
- List of patients with adverse events
- List of patients with adverse reactions
- List of patients with adverse reactions excluded from safety analysis
- List of patients with excluded adverse reactions included in safety analysis
- List of patients with adverse reactions among contraindicated patients
- List of patients with serious adverse reactions

- List of patients with serious adverse events
- List of deaths
- List of efficacy evaluation
- List of complications corresponding to risk factors for aggravation of infection caused by SARS-CoV-2
- List of concomitant drug therapies for infection caused by SARS-CoV-2
- List of concomitant non-drug therapies for infection caused by SARS-CoV-2
- List of SARS-CoV-2 viral tests
- List of body temperature and percutaneous arterial oxygen saturation (SpO_2)

In addition, forms necessary for re-examination application (PSEHB/PED Notification No. 0325-10 dated March 25, 2020 issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) will be prepared.

Furthermore, forms necessary for periodic safety reports (PSEHB/PED Notification No. 1128-5 dated November 28, 2017 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) will be prepared.

10. APPENDICES

10.1. Appendix 1: Handling of Efficacy-related Questionnaire Items in the Identification of Efficacy Analysis Sets

Table 1. Identification of Efficacy Analysis Sets 1 and 2

Case	Status of CRF entry			Safety Analysis Set‡	Efficacy Analysis Set 1†‡			Efficacy Analysis Set 2†‡			
	Adverse event page	Hospitalization status page	Efficacy evaluation page	Inclusion/ exclusion (Reason)	Inclusion/ exclusion (Reason)	Evaluable		Inclusion/ exclusion (Reason)	Evaluable		
						Deaths	Severity related		Deaths	Hospitalization or death	Severity related
1	Yes	Yes	Yes	Included	Included	Yes	Yes	Included	Yes	Yes	Yes
2	**No**	Yes	Yes	**Excluded (AE information)**	Included	Unknown	Yes	Included	Unknown	Yes (only hospitalization events present) or unknown	Yes
3	Yes	**No**	Yes	Included	Included	Yes	Yes	Included	Yes	Yes (only death events present) or unknown	Yes
4	Yes	Yes	**No**	Included	Included	Yes	Unknown	Included	Yes	Yes	Unknown
5	**No**	**No**	Yes	**Excluded (AE information)**	Included	Unknown	Yes	Included	Unknown	Unknown	Yes
6	**No**	Yes	**No**	**Excluded (AE information)**	Included	Unknown	Unknown	Included	Unknown	Yes (only hospitalization events present) or unknown	Unknown
7	Yes	**No**	**No**	Included	Included	Yes	Unknown	Included	Yes	Yes (only death events present) or unknown	Unknown
8	**No**	**No**	**No**	**Excluded (AE information)**	**Excluded (Efficacy information)**	NA	NA	**Excluded (Efficacy Set 1)**	NA	NA	NA

AE, adverse event; NA, not evaluated due to exclusion from population

‡ For the CRF pages to be used to identify the population other than the adverse event page, hospitalization status page, and efficacy evaluation page, it is assumed that there are no items meeting the exclusion criteria.

10.2. Appendix 2: Data Extraction Details

Table 2. Definitions of Acceptable Windows for Timing

Timing	Endpoint	Definition [acceptable window]
At the start of treatment	Efficacy endpoints, viral load, body temperature, percutaneous arterial oxygen saturation	From 30 days prior to the date of first dose in this study (start date of treatment) to the start date of treatment
During the observation period	Safety endpoints, efficacy endpoints, viral load, body temperature, percutaneous arterial oxygen saturation, concomitant drug therapy, and non-drug therapy	Start date of treatment to Day 28 after the end of treatment
End date of the observation period	Efficacy endpoints	Primary definition: Up to Day 28 after the end of treatment Secondary definition 1: Up to 42 days after the end of treatment Secondary definition 2: Entire period

10.3. Appendix 3: Data Entries Related to Efficacy Endpoints and Their Handling, and Assessment of Endpoints

Table 3. Worsening of Severity and Highest Severity of Infection Caused by SARS-CoV-2

<table>
<tr><th rowspan="4">Symptoms at the start of treatment with this drug</th><th rowspan="4">Severity at the start of treatment with this drug</th><th colspan="8">Worsening of severity: Highest severity</th></tr>
<tr><th colspan="8">Worsening of severity during the observation period</th></tr>
<tr><td>Absent</td><td colspan="5">Present</td><td>Unknown</td></tr>
<tr><th colspan="8">Highest severity</th></tr>
<tr><td>NA</td><td>Mild</td><td>Moderate I</td><td>Moderate II</td><td>Severe</td><td>Unknown</td><td>NA</td></tr>
<tr><td>Absent</td><td>NA</td><td>Absent: NA</td><td>Present: Mild</td><td>Present: Moderate I</td><td>Present: Moderate II</td><td>Present: Severe</td><td>Present: Unknown</td><td>Unknown: NA</td></tr>
<tr><td rowspan="4">Present</td><td>Mild</td><td rowspan="3" colspan="4">Case 1</td><td rowspan="3">Case 2</td><td rowspan="5"></td></tr>
<tr><td>Moderate I</td></tr>
<tr><td>Moderate II</td></tr>
<tr><td>Severe</td><td>Severe at the start: NA</td><td colspan="5">Case 3</td></tr>
<tr><td>Unknown</td><td>Absent: NA</td><td colspan="6">Case 4</td></tr>
<tr><td>Unknown</td><td>NA</td><td colspan="7">Case 5</td></tr>
</table>

NA: not applicable

Discrepancies between evaluations at the start of treatment with this drug and during the observation period are subject to re-investigation, but the reasons for being subject to re-investigation and handling of cases where there is no change as a result of re-investigation are shown below.

- Case 1: Assessed as "Unknown: NA" because the highest severity is lower than the severity at the start of treatment with this drug.
- Case 2: Assessed as "Unknown: NA" because the severity during the observation period is unknown. However, if the severity is considered to have worsened during the observation period, it will be handled as "Present: Unknown" for analysis. In addition, when the severity at the start is moderate I, the highest severity will be considered as "moderate II or severe (indistinguishable)" for analysis, and when the severity at the start is moderate II, the highest severity will be considered as "Present: Severe" for analysis.
- Case 3: Assessed as “Unknown: NA” because the severity is severe at the start but worsened during the observation period. However, if the severity is assessed as severe at the start, worsening of severity will be handled as "sever at the start" and the highest severity will be handled as NA.
- Case 4: Assessed as "Unknown: NA" because the severity at the start is unknown. However, if the severity is judged to have worsened during the observation period, worsening of severity will be handled as "present" and the highest severity entered will be the highest severity for analysis.
- Case 5: Assessed as "Unknown: NA" because the symptoms at the start are unknown.

Table 4. Resolution of symptoms from the start of treatment with this drug as of the end date of the observation period

Symptoms at the start of treatment with this drug	Resolution of symptoms		
	Symptoms at the end of the observation period		
	Absent	Present	Unknown
Absent	No symptoms at the start of treatment with this drug	Absent	Unknown
Present	Present		
Unknown	Unknown		

Table 5. Improvement in severity from the start of treatment with this drug as of the end date of the observation period

Symptoms at the start of treatment with this drug	Severity at the start of treatment with this drug	Improvement in severity						
		Symptoms at the end date of the observation period						
		Absent	Present					Unknown
		Severity at the end date of the observation period						
		NA	Mild	Moderate I	Moderate II	Severe	Unknown	NA
Absent	**NA**	No symptoms at the start of treatment with this drug						
Present	**Mild**	Present	Absent					
	Moderate I							
	Moderate II							
	Severe							
	Unknown							
Unknown	**NA**	Unknown						