XEVUDY
General Drug Use Investigation
(SARS-CoV-2 Infection)

Protocol

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1. Objectives

The objective of this study is to collect and assess the following information about safety and clinical outcomes of Xevudy in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who have risk factors for progression to severe SARS-CoV-2 infection and do not require oxygen administration (OA) in daily clinical practice.

Primary endpoint;

- Occurrence status of adverse drug reactions (ADRs)

Secondary endpoint;

- Proportion of non-responders, and distribution and transition of vital signs and clinical symptoms

2. Safety Specification

In this study, the concern included in the safety specification is as follows;

- Serious Hypersensitivity such as Anaphylaxis, Infusion Reaction

3. Target Population

Among patients with SARS-CoV-2 infection which is Xevudy's indication, patients who have risk factors for progression to severe SARS-CoV-2 infection and do not require OA for SARS-CoV-2 infection at the beginning of Xevudy administration and receive Xevudy for the first time will be included in the study.

4. Target Sample Size and Rationale

1) Target number of patients: 630 (as enrolled patients)
2) Rationale:
   "Serious Hypersensitivity such as Anaphylaxis and Infusion Reaction" is an important identified risk on Risk Management Plan (RMP) for Xevudy. The incidence rate of patients experiencing events correspond to Hypersensitivity (narrow) in Standardised MedDRA Queries (SMQs) within Xevudy group for 29 days was 1.7% (9/523 patients) in the global phase II/III clinical study for patients with mild to moderate infections (COMET-ICE Study). A total of 600 patients as a safety analysis set is required to monitor the incidence rate of event-experiencing patients in the post-marketing surveillance (PMS), with estimation accuracy that enables a power of ≥80 % to detect an odds ratio of 2 for the 1.7% threshold, in case where there is the twofold real risk of the threshold. Accordingly, it is thought to be possible to examine the incidence rate in the drug use investigation of 630 patients.

5. Planned Number of Medical Institutions by Department

Approximately 30 medical institutions which provide SARS-CoV-2 infection treatment, mainly medical institutions designated for infectious diseases, regional medical care support hospitals and special functioning hospitals

6. Study Period

1. Study conduct

1） Study period: November 2021 to October 2023

2） Observation period:

The observation period per patient will be between Day 1 to 29 counting the date of Xevudy administration as Day 1 (28 days from the day following Xevudy administration or Day 2). If inpatients have been discharged/transferred from hospital before Day 29, they will be observed until the discharge/transfer date. For outpatients, the observation will be conducted on Day 1 only.

3) Scheduled enrolment period: January 2022 to June 2023

However, if the number of enrolled patients has reached the target sample size, enrolment may be terminated even before the completion of the above-mentioned scheduled enrolment period.

2. Study end

Time for final analysis to complete: June 2024

Time for final report writing to complete: December 2024

7. Study Methods

In this study, an electronic data capture (EDC) system will be used to enroll patients and collect data.

1. Request and contract for the study
   1) The medical representative (MR) will explain the objectives, target population, study items, study methods, etc. to the planned physicians for the study, etc. at the medical institutions to which Xevudy is supplied and will request them to cooperate with the study.
   2) When the medical institutions agree to participate in the study, the Written Contract should be concluded with the heads of the medical institutions (e.g. directors, etc.) before the start of the study.
2. Issuance of user identification (ID) and password

   The investigator will receive an ID and a password required for entry into the EDC system after conclusion of the contract.
3. Obtaining informed consent

   The investigator will provide diagnosis and prescription based on daily medical practice and will explain to the patient (and/or patient's representative) who receives Xevudy for the first time and will obtain the informed consent from him/her.

   The investigator will sufficiently explain participation in the study and publication of the study results to the patient (and/or patient's representative) using the Informed Consent Form, and obtain a signature or name/seal and the date of informed consent from the patient (and/or patient's representative), and check a box for Informed Consent "Yes" on the Enrolment Form. The Informed Consent Form obtained from the patient (and/or patient's representative) will not be submitted to the MR.

   If the patient (and/or patient's representative) requests to withdraw the informed consent during the study period, the investigator should notify to the study sponsor (MR, etc.) with a document.
4. Enrolment of target population

   The study will be conducted using a central enrolment method.
   1) For "3. Target Population" who receive Xevudy after conclusion of the contract with the informed consent from the patient (and/or patient's representative), the investigator will enter the patient information, etc. into the EDC system to enroll within 14 days from the date of Xevudy administration (Xevudy administration date is regarded as Day 1). The personal information, such as the name, address, date of birth, medical record number, initials of patients, must not be entered into the EDC system.

2) If the number of enrolled patients has reached the number of contracted patients, enrolment into the study will be terminated.

5. Data collection and entry into the electronic data capture (EDC) system

1) The investigator will confirm the study items, such as the characteristics of enrolled patients.

2) The investigator will confirm the safety and clinical outcomes information, pregnant status information by the end of observation period, and enter the data into the EDC system.
The safety and effectiveness information (medical interview, telephone, etc.) will be monitored within the scope of routine clinical practice.

3) At the end of the observation period of enrolled patients, the investigator will enter the obtained information into the EDC system to transmit. The personal information, such as the name, address, date of birth, medical record number, initials of patients, must not be entered into the EDC system.

8. Study Items

The investigator will collect the information about the following items, etc. according to the following schedule as far as possible and enter it into the EDC system within the scope of routine clinical practice.

1. Study schedule

The timings of when to observe/assess the main study items are as follows.

Study item \ Study period	4 weeks prior to administration	Day 1	-	Day 15	Day 22	Day 29
		If inpatients have been discharged/transferred from hospital before Day 29, they will be observed until the discharge/transfer date. For outpatients, the observation will be conducted on Day 1 only.				
Patient characteristics		●				
Variant test		●				
Vaccination status against SARS-CoV-2 infection		●				
Administration status of Xevudy		●				
Pre-treatment medications	←					
Concomitant medications		←	—	—	—	→
Combination therapies for exacerbation of SARS-CoV-2 infection[1, 3]		←	—	—	—	→
Admission into HCU or ICU[3]		←	—	—	—	→
Vital[2, 3]		←	—	→	●	●
Clinical symptoms[3]		←	—	→	●	●
Status at the end of the observation		←	—	—	—	→
Pregnancy/Breastfeeding		←	—	—	—	→
AEs		←	—	—	—	→

1: Invasive mechanical ventilation (IMV) management, extracorporeal membrane oxygenation (ECMO), oxygen administration (OA), etc.

2: Body temperature, percutaneous oxygen saturation (SpO2), if measured.

3: Inpatient only.

2. Study items

1. Information about a medical institution
   Name of a medical institution, department, investigator
2. Patient characteristics (at the time of Xevudy administration or Day 1)
   ID number, gender, year of birth, date of Xevudy administration, reason for Xevudy use, types of risk factors for progression to severe SARS-CoV-2 infection, confirmation of informed consent, hospitalization status, date of sampling for nucleic acid detection tests/antigen tests showing positive, variants test status and variant type, severity[1], onset date of symptom (If a symptom is identified. If multiple symptoms are identified, record the onset date of the first symptom), weight and height, presence or absence of comorbidities (renal impairment, hepatic impairment, allergy, other) and name of comorbidities, smoking history, OA status for SARS-CoV-2 infection, OA status for diseases except for SARS-CoV-2 infection, reason for OA and baseline oxygen flow rate (L/min)
   To protect the confidentiality regarding ID of an individual patient, the ID number should be a unique number assigned to an individual patient by the investigator, etc.
   In this study, any disease/symptom which is present at the time of Xevudy administration except for the reason for Xevudy use will be handled as a “comorbidity”.
3. Vaccination status against SARS-CoV-2 infection
   Vaccinated or unvaccinated against SARS-CoV-2 infection, year, month and date of vaccination before Xevudy administration (If multiple doses of a vaccine are required, record the year, month and date of vaccination for all doses)
4. Pre-treatment medications (during 4 weeks prior to Xevudy administration)
   Presence or absence of pre-treatment medications, name of medications, whether or not a patient started and finished them prior to Xevudy’s administration, and reason for administration
5. Administration status of Xevudy
   Date of Xevudy administration, dose (mg as a single infusion), administration route, infusion rate (mL/hr)
6. Concomitant medications
   Presence or absence of concomitant medications, name of medications, whether or not a patient started and finished them prior to Xevudy’s administration, reason for administration
7. <Inpatient only> Combination therapies for exacerbation of SARS-CoV-2 infection except for medications
   Whether or not combination therapies for exacerbation of SARS-CoV-2 infection are introduced, name of therapies (invasive mechanical ventilation (IMV) management, extracorporeal membrane oxygenation (ECMO), OA, etc.), name of therapies and date of combination therapies introduced, oxygen flow rate (maximum flow rate during the observation period) (L/min) and date of maximum flow rate introduced
8. <Inpatient only> Vital signs
   Highest body temperature (°C) and lowest percutaneous oxygen saturation (SpO_2) (%) and date of measurement at Day 1, Days 2-15 (every day), Day 22, Day 29 and the discharge/transfer date. On Day 1, the highest body temperature and the lowest SpO_2 will be selected from values which are measured before Day 1.

[1] See Guidelines for Diagnosing Patients with Novel Coronavirus Infection (COVID-19) (Guidelines Review Committee).

9. <Inpatient only> Clinical symptoms (cough without sputum (nonproductive cough), cough with sputum (productive cough), fatigue, dysgeusia, olfactory dysfunction, headache, dyspnea, sore throat, diarrhea, nasal discharge, arthralgia/myalgia), symptom of pneumonia
   Presence or absence of clinical symptoms and date of observation at Day 1, Days 2-15 (every day), Day 22, Day 29 and the discharge/transfer date. If any of these clinical symptoms have been identified at the date of each observation, select the clinical symptoms applicable to these.
   If a symptom is not identified at Day 1 but newly occurs after Day 1 or a symptom is identified at Day 1, disappears after Day 1 and reoccurs, the symptom should be recorded into adverse events (AEs) section of the case report form (CRF) in case where it is assessed as an AE.
10. <Inpatient only> Admission status into high care unit (HCU) or intensive care unit (ICU) during observation period
    Whether or not a patient is admitted into HCU or ICU and date of admission
11. Status at the end of the observation
    End date of observation, inpatient outcome (hospitalization, discharge, transfer, and the reason), and whether or not a patient has died from exacerbation of SARS-CoV-2 infection and the reason
12. Pregnancy
    (For female patients) whether or not a patient is pregnant during the observation period, estimated delivery date
    In addition, the follow-up investigation should be conducted for a mother and her foetus as far as possible regarding the course of delivery, spontaneous abortion, elective abortion, and AEs, etc.
13. Breastfeeding
    (For female patients) Whether or not a patient feeds breast milk during the observation period
14. Adverse event (AEs)
    Presence or absence of AEs after Xevudy administration, diagnosis or symptoms, occurrence date, outcome of AEs, outcome date (outcome date confirmed), seriousness, reason for assessing as serious, relationship to Xevudy, factors suspected of being related to AEs except for Xevudy
    i). To grasp the safety specification and ADRs/AEs, the investigator will collect the information about all AEs (e.g., a disease, symptom, abnormal laboratory value) occurring after Xevudy administration, regardless of whether or not Xevudy is related to an AE. Considering whether or not the possibility of a reasonable relationship to Xevudy is present, the relationship to Xevudy will be assessed as “related” or “not related” by the investigator. The AEs assessed as “related” to Xevudy will be handled as an “ADR” suspected of being caused by Xevudy.
    ii). Among reported AEs, evens corresponding to the following A or B will be handled as a concern in the safety specification, "Serious Hypersensitivity such as Anaphylaxis and Infusion Reaction ".
        A) Events which exclude both High Level Term (HLT) "Injection Site Reactions " and HLT "Infusion Site Reactions " from "Hypersensitivity (narrow)" in SMQs
        B) "Anaphylactic reaction" (broad) in SMQs

9. Analysis Items and Methods

The detailed content of analysis will be separately specified in the Statistical Analysis Plan.

1. Analysis items
   1) Patient disposition-related matters
      i) Number of enrolled patients and number of patients whose CRF data are collected and locked
      ii) Number of patients included in the safety analysis set and number of patients included in the clinical outcomes analysis set, numbers of patients excluded from safety and clinical outcomes analysis set and the reasons for exclusion
   2) Safety-related matters
      i) Occurrence of ADRs (type and seriousness of ADRs, and incidence rate of patients with ADRs, etc.)
      ii) Occurrence of an event defined as a concern included in the safety specification
   3) Clinical outcomes-related matters
      i) <Inpatient only>Proportion of non-responders
      Among the patients who can be assessed for the following items a) to e) from Day 1 to the end of observation period, the following patients will be defined as "not effective" if applicable to any of a) to e). The proportion of non-responders is the proportion of patients assessed as "not effective" in the clinical outcomes analysis set.
         a) Patients who receive oxygen at a rate of <5L/min as a combination therapy for exacerbation of SARS-CoV-2 infection
         b) Patients who receive any of the following combination therapies for exacerbation of SARS-CoV-2 infection
            - Non-invasive positive pressure ventilation (NPPV)
            - Invasive mechanical ventilation (IMV) management
            - Extracorporeal membrane oxygenation (ECMO)
         c) Patients who require admission to HCU or ICU for exacerbation of SARS-CoV-2 infection in medical institutions with HCU or ICU
         d) Patients who are transferred to another hospital for exacerbation of SARS-CoV-2 infection to receive the treatments of a) to c) mentioned above
         e) Patients who result in death for exacerbation of SARS-CoV-2 infection
      ii) <Inpatient only> Distribution and transition of vital signs (Day 1, Days 2-15, Day 22, Day 29, discharge/transfer date)
      iii) <Inpatient only> Distribution and transition of clinical symptoms (Day 1, Days 2-15, Day 22, Day 29, discharge/transfer date)
2. Analysis methods
   1) Safety
      i). The incidence rate of ADR patients will be calculated throughout the whole period, at Day 1, Days 2-15, Day 22, Day 29.
      ii). The incidence rate of ADR-experiencing patients per 100 patient-years will be calculated along with 95% exact Poisson confidence intervals using chi-square distribution.
   2) Clinical outcomes

i) The proportion of non-responders will be calculated (from Day 1 to the end of the observation period). The proportion of non-responders by sampling period for nucleic acid detection tests/antigen tests showing positive will be calculated.

ii) The proportion of patient outcome at the end of the observation period in patients other than non-responders was be calculated.

iii) Summary statistics for vital signs will be calculated based on values at the time of measurement (Day 1, Days 2-15, Day 22, Day 29, discharge/transfer date). Also, summary statistics for vital signs by sampling period for nucleic acid detection tests/antigen tests showing positive will be calculated.

iv) For clinical symptoms, the incidence rate of patients with or without them will be calculated over time. Also, the incidence rate by sampling period for nucleic acid detection tests/antigen tests showing positive will be calculated.

3) Covariate consideration

The Robust (modified) Poisson regression model will be used to calculate the risk ratio and 95% confidence interval for each factor likely to affect safety (incidence rate of ADR patients) and clinical outcomes (proportion of non-responders), and to explore risk factors. For exploration of risk factor as appropriate, the unadjusted risk ratio and its 95% confidence interval will be calculated in univariate analysis. In the multivariate analysis, Spearman's correlation coefficient will be used first to confirm whether or not multicollinearity exists between factors, the missing values for each factor will be considered to select variables to be included in the model, and then the adjusted risk ratio and its 95% confidence interval will be calculated.

10. Organizational Structure

Refer to AT1

11. Name, Address of the Outsourcees, and the Scope of Outsourced Operations

1. Enrolment and data management
   Outsourcee: CMIC Co., Ltd. (1-1-1 Shibaura, Minato-ku, Tokyo)
   Scope: patient enrolment, EDC system development, data cleaning, other related operations
2. Statistical analysis
   Outsourcee: CMIC Co., Ltd. (1-1-1 Shibaura, Minato-ku, Tokyo)
   Scope: statistical analysis, other related operations

12. Scheduled Timing to Be a Milestone for Assessing the Status and Results in the Study or Reporting to the Pharmaceuticals and Medical Devices Agency (PMDA) and Rationale

- At the time of Periodic Safety Reports: consideration will be comprehensively given to the safety and clinical outcomes information.
- At the time of re-examination application: the final report will be prepared/submitted, based on the results of tabulation and analysis obtained from the locked data of all collected CRFs.

13. Additional Measures that Have a Potential to Be Taken Depending on the Study Results and the Decision Criteria for the Start

The RMP, including the following, will be reviewed at the timings to be a milestone.

- Regarding the safety specification, if the incidence rate of patients experiencing ADRs, peak occurrence period and risk factors become visible as an ADR caused by Xevudy, the necessity for revising the Package Insert and study materials will be considered as appropriate.
- Including whether or not a new concern in the safety specification is present, the necessity for changes in the content of study plan will be considered.
- The necessity for creation of the Risk Minimization Plan for a new concern in the safety specification will be considered.

14. Publication of the Study Results

Regarding the results of the study, the paper will be published as a final report for the purpose of "proper use" and "safety assurance" in accordance with GSK Policy, and the information will be provided to clinical sites as an interim report as appropriate.

The study results which have been reported to the Pharmaceuticals and Medical Devices Agency (PMDA) will be disclosed upon request, based on the Information Disclosure Law. The study results or its summary will be posted on the home pages of the PMDA and overseas regulatory authorities-designated institutions, ClinicalTrials.gov, GSK Study Register and the home page of GSK. In any case, the information about privacy of a patient and an investigator will never be disclosed.

15. Other Requirements

1. Protocol revision

   The progress in the study, the numbers of patients excluded from analysis, occurrence of unexpected/serious ADRs, large increase in occurrence of specific ADRs and validity of the study items, etc. will be timely grasped during the study period, and the Protocol will be reviewed and revised if required.

   If the content of the Protocol in the study has been changed, the written submission should be made to the PMDA in advance, except for minor changes.

2. Measures to be taken in detecting issues and concerns

   If issues, etc. have been detected from the results of assessment/analysis during the study period or after completion of the study, consideration will be given on whether or not the PMS should be newly conducted, as appropriate.

3. Report of the results of the study

   The result of the study for safety and clinical outcomes will be reported to the Minister of Health, Labour and Welfare as the periodic safety reports every six months for one year after the date designated by Minister of Health, Labour and Welfare and yearly thereafter, based on Article 63 of the "Ministerial Ordinance for Enforcement of the Act for Ensuring etc. the Quality, Efficacy, and Safety of Drugs, Medical Devices, etc. (Ordinance of the Ministry of Health and Welfare No. 1 of 1961".

16. Attachments

1) GPSP Organization chart AT1
2) XEVUDY General Drug Use Investigation

Implementation Guidance AT2

3) XEVUDY General Drug Use Investigation Enrolment Form and Case Report Form AT3

Adverse Events (AEs)

Requests in experiencing an AE

- For a patient experiencing an AE, further detailed investigation may be conducted as appropriate. In such case, your cooperation would be appreciated.
- If a patient has experienced an AE, contact our MRs immediately.

1. Adverse Events (AEs)

   The term "AE" means any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a relationship to this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory value, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

   Examples regarded as an AE :

   - Exacerbation of any chronic or intermittent symptom being present before the start of the study (including increase in frequency or severity of symptoms). Any case where a target disease and a comorbidity worsen **unexpectedly**
   - Any symptom being newly detected or diagnosed after the start of Xevudy administration (included as an AE if it has been detected or diagnosed after Xevudy administration, even though it may have already been present before the start of the study)
   - Any sign, symptom, or sequela originating from a suspected interaction
   - Any symptom causing any medical or surgical treatment to be required (eg : endoscopy, appendicectomy, etc.)
   - Any sign, symptom, or sequela originating from a suspected overdose of Xevudy or concomitant medications (An overdose itself should not be reported as an AE or SAE) However, a deliberate overdose intended for suicide/self-injury should be reported, regardless of the presence/absence of a sequela
   - Any abnormal laboratory value (hematology test, biochemical test, urine test) or any other abnormal safety assessment item (eg : electrocardiogram, X-ray test, measurement of vital signs) (including worsening from baseline) when an investigator judges a patient's condition as clinically significant **beyond the expectable range** based on medical and scientific judgment

   Examples not regarded as an AE :

   - Any progress, sign or symptom of a target disease or disorder and an **expected** disease or disorder
   - Any medical or surgical treatment (eg : endoscopy, appendicectomy). The symptom which needs these treatments should be regarded as an AE
   - Any case where no unfavourable medical occurrence happens (social and /or hospitalisation in convenience, etc.)
   - Any disease and condition,if identified or detected before the start of the study, the changes in them are within the expected range of daily changes or does not worsen

- Any change in abnormal laboratory values and any other safety assessment items, etc. related to a target disease or a comorbidity

2. Adverse Drug Reactions (ADRs)
   All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. The phase “response to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Unlike an AE, an ADR features the fact that a relationship between a medicinal product and occurrence of an AE is suspected.

3. Serious Adverse Events (SAEs)
   An SAE means any untoward medical occurrence associated with the use of a drug that at any dose :

   1) results in death
   2) is life-threatening[1]
   3) requires inpatient hospitalisation or prolongation of existing hospitalisation
   4) results in persistent or significant disability/incapacity
   5) is a congenital anomaly/birth defect
   6) is another event or reaction, if judged to be a medically important[2]