Clinical Study Protocol

NCT Number: NCT03729609

Title: General Drug Use Surveillance Protocol General Drug Use Surveillance for ADCETRIS Intravenous Infusion 50 mg “Untreated CD30-Positive Hodgkin's Lymphoma”

Study Number: C25018

Document Version and Date: Version 8.0 / 12-Sep-2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

Note; This document was translated into English as the language on original version was Japanese.

General Drug Use Surveillance Protocol
General Drug Use Surveillance for ADCETRIS Intravenous Infusion 50 mg "Untreated CD30-Positive Hodgkin's Lymphoma"

Survey sponsor	**Takeda Pharmaceutical Company Limited**
Protocol No.	**C25018**
Edition	**Version 8.0**
Date of preparation	**September 12, 2023**

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[redacted]

1.0 BACKGROUND

Information about the safety of ADCETRIS intravenous infusion 50 mg (hereinafter, ADCETRIS) in combination with doxorubicin hydrochloride, vinblastine sulfate and dacarbazine (hereinafter, AVD) in Japanese patients is limited. Compared to ADCETRIS monotherapy, the incidences of neutropenia and febrile neutropenia are higher with combination therapy with ADCETRIS plus these agents. Therefore, it was decided that additional pharmacovigilance activities for neutropenia and febrile neutropenia were necessary in order to confirm the occurrence status in actual setting of use in Japan.

Thus, a drug use survey (hereinafter, this survey) was planned in patients with untreated CD30-positive Hodgkin lymphoma in daily clinical practice.

This survey is conducted in accordance with relevant regulatory requirements including the GPSP Ordinance.

2.0 PURPOSE

Evaluate the occurrence status of neutropenia and febrile neutropenia with ADCETRIS used in combination with AVD in patients with untreated CD30-positive Hodgkin's lymphoma in daily clinical practice.

3.0 SCHEDULED NUMBER OF CASES AND RATIONALE

3.1 SCHEDULED NUMBER OF CASES

100 (as Safety Analysis Set)

3.2 RATIONALE

The global phase 3 study in patients with untreated advanced classical Hodgkin's lymphoma (C25003 study) indicated that the incidence of the adverse event of febrile neutropenia in patients who received G-CSF for primary prevention was 11%, and the incidence of the adverse event of neutropenia of Grade 3 or higher was 29%.

In the special drug use-result survey of ADCETRIS in patients with relapsed or refractory CD30-positive Hodgkin’s lymphoma and anaplastic large cell lymphoma, the number of Hodgkin’s lymphoma patients with the adverse event of febrile neutropenia was 6. It is therefore considered necessary to collect at least 6 cases of the adverse event of febrile neutropenia in this survey.

Assuming that the incidence of the adverse event of febrile neutropenia is 11%, a sample size of 93 patients is required to detect at least 6 cases of the adverse event of febrile neutropenia at a ≥95% probability. The sample size was thus determined to be 100. On the assumption that the incidence of the adverse event of neutropenia of Grade 3 or higher is 29%, ≥22 cases of neutropenia of Grade 3 or higher will be observed at a ≥95% probability if 100 cases are collected.

4.0 PATIENTS TO BE SURVEYED

Patients with Hodgkin's lymphoma will be included in this survey. However, patients must meet the following inclusion criteria and none of the exclusion criteria. The Precautions listed in the package insert should be referred.

4.1 INCLUSION CRITERIA

Patients who meet the following criteria will be included in this survey.

[1] Untreated patients

[2] CD30-positive patients

[3] Patients on concomitant ADCETRIS and AVD

4.2 EXCLUSION CRITERIA

Patients who meet the following criteria will be excluded from this survey.

Patients contraindicated for ADCETRIS

5.0 DOSAGE AND ADMINISTRATION

In combination therapy with AVD, the usual adult dosage for intravenous administration is 1.2 mg/kg (weight) as brentuximab vedotin (genetical recombination) once every 2 weeks for up to 12 doses. The dose may be reduced appropriately according to the patient's condition. The Precautions listed in the package insert should be referred for details.

6.0 SCHEDULED NUMBER OF MEDICAL INSTITUTIONS BY CLINICAL DEPARTMENT

Department of hematology etc. Approximately 100 medical institutions

7.0 METHOD

7.1 OBSERVATION PERIOD

Period from the start of ADCETRIS to 2 weeks after the completion of 12 doses (once every 2 weeks)[note)]

Note) If a patient receives less than 12 doses of ADCETRIS, the period will be up to 2 weeks after the discontinuation of ADCETRIS.

* Rationale for observation period

In the ADCETRIS + AVD group in C25003 study, the number of patients with the event of neutropenia, neutrophil count decreased and febrile neutropenia after the initial dose and the number of patients with the initial onset in each Cycle were highest in Cycle 1 for both of all Grades and Grade 3 or higher, which decreased over time as the cycles went on. However, still in Cycle 6 (period between 11th dose and 2 weeks after the 12th dose), the number of patients with the initial onset was 2 for neutropenia and 5 for febrile neutropenia. The number of patients with the event of Grade 3 or higher was 64 for neutropenia, 8 for febrile neutropenia,

and 18 for neutrophil count decreased.

Based on the above, it was considered necessary to observe the occurrence status of myelosuppression (neutropenia, febrile neutropenia) set as safety specification for this survey until 2 weeks after the completion of 12 doses, the maximum number of doses specified in the DOSAGE AND ADMINISTRATION.

7.2 REQUEST TO AND CONTRACT WITH MEDICAL INSTITUTIONS

The person in charge from Takeda Pharmaceutical Company Limited (hereinafter, "Takeda's person in charge") should, when requesting a medical institution and physician to conduct this survey, conclude a written contract with the medical institution.

7.3 PATIENT CONSENT

The investigator should, before registering patients, explain the details of the informed consent form to patients (or their legal representatives) and obtain oral or written consent from patients (or their legal representatives) to provide information to this survey.

For written consent, patients (or their legal representatives) should sign and date the informed consent form. The investigator should retain the original signed and dated informed consent form.

The informed consent form should include information on the outline of this survey and patient's personal information as well as its handling, and explain that patients may discontinue the participation in this survey at any time without explaining the reason and suffering any therapeutic disadvantage.

Patients who have provided consent will be assigned an identification number.

7.4 PATIENT ENROLLMENT METHOD

The "Central Registration Method" by post should be used.

The investigator or a person appointed by the investigator* should send "Patient Registration Sheet" via post to the Central Registration Center by 30 days after the start of treatment with ADCETRIS (the day of the first dose is counted as "Day 0" and the following day as "Day 1").

The day of the postmark is deemed the day of patient enrollment.

* The "person appointed by the investigator" refers to those who belong to the relevant medical institution (including those who are contracted with the medical institution for assignments, such as contracted CRC) and who have been designated beforehand by the investigator to execute assignments relating to this survey under the instruction of the investigator. The physician responsible for the survey conduct (one person per medical institution or clinical department, to be determined at the time of concluding a contract) will prepare documentation that indicates the designation and the date of designation (in any form), sign or seal and submit it to the Takeda's person in charge before a person appointed by the investigator starts the assignments such as patient enrollment.

7.5 PREPARATION AND SUBMISSION OF SURVEY SHEETS

Paper-based survey sheets should be used to collect information.

The investigator or a person appointed by the investigator should prepare a survey sheet for all the enrolled patients promptly after completion of the observation period of each patient, and the investigator should sign or print his/her name on and seal the sheet to submit to Takeda Pharmaceutical Company Limited.

For patients in whom ADCETRIS has been discontinued due to some reasons in the middle of the observation period, the investigator or a person appointed by the investigator should prepare a survey sheet promptly after the completion of necessary observation, and submit to Takeda Pharmaceutical Company Limited.

8.0 SCHEDULED PERIOD OF SURVEY

Survey period : November 2018 to December 31, 2022

Patient registration period : November 2018 to December 31, 2021[note)]

Survey Completion date (Estimated completion date of Statistical Analysis): planed as October 30, 2023

Note) No patients will be registered after January 1, 2022 even if the patient has started treatment with ADCETRIS before December 31, 2021.

If it is estimated that the overall number of patients registered to this survey reaches the planned sample size (as Safety Analysis Set) before December 30, 2021, the patient registration will be closed before the end of patient registration period. If the patient registration period is shortened, this survey period will be changed according to the shortened duration.

9.0 SURVEY ITEMS

The investigator or a person appointed by the investigator should include the following items in the Patient Registration Sheet and Survey Sheet. The schedule of this survey is indicated in Appendix 1.

9.1 PATIENT REGISTRATION

1) Survey items

The start date of treatment with ADCETRIS, patient identification number, gender, age, presence/absence of (verbal or written) consent, assessment results of the inclusion and exclusion criteria

2) Survey period

At the time of patient registration

9.2 PATIENT CHARACTERISTICS

1) Survey items

Time of diagnosis of Hodgkin's lymphoma, lesion, clinical stage (Ann Arbor Staging),

presence/absence of B symptoms, ECOG Performance Status, therapeutic category, complications (presence/ absence and details), medical history (presence/absence and details), height, weight, presence/absence of pregnancy/lactation (for women only)

2) Survey period

At the start of ADCETRIS

9.3 TREATMENT

1) Survey items

Administration status of ADCETRIS and AVD, reason for the discontinuation of ADCETRIS, administration status of medications other than ADCETRIS and AVD to the underlying disease (presence/absence and name of the drug, duration of administration), administration status of drugs used to prevent infections (presence/absence and name of the drug, duration of administration), administration status of G-CSF (presence/absence and name of the drug, duration and purpose of administration)

2) Survey period

Period from the start of ADCETRIS to 2 weeks after the completion of 12 doses or the discontinuation of ADCETRIS

9.4 TUMOR RESPONSE

1) Test items

Best response should be assessed as CR, CRu (if no PET is performed), PR, SD or PD in accordance with the Revised response criteria (see Appendix 2) based on the result of CT and PET scan of the neck, chest, abdomen, and pelvis.

2) Survey period

Period from the start of ADCETRIS to 2 weeks after the completion of 12 doses or the discontinuation of ADCETRIS (but until before the start of subsequent treatment)

9.5 OBSERVATION ITEMS

1) Observation items

Presence/absence of pregnancy during the observation period (for women only)

2) Survey period

Period from the start of ADCETRIS to 2 weeks after the completion of 12 doses or the discontinuation of ADCETRIS

9.6 ADVERSE EVENTS

1) Events subject to survey

The following event is determined as the safety specification. Information of those of Grade 3 or higher will be collected.

- Myelosuppression (neutropenia, febrile neutropenia)

* Rationale

Among the important identified risks in the Risk Management Plan, myelosuppression (neutropenia, febrile neutropenia) was determined as safety specification based on the following reasons: The global phase 3 study in patients with untreated advanced classical Hodgkin's lymphoma (C25003 study) indicated that the incidence of febrile neutropenia was higher in the concomitant ADCETRIS and AVD group than the comparator ABVD group. In light of this fact, the (draft) important precautions of ADCETRIS describe that use of G-CSF including prophylactic administration (primary prevention) should be considered in using ADCETRIS in combination with AVD. Control of neutrophil count is important to continue administration of ADCETRIS (including resumption after interruption). The profile of this event (administration status of ADCETRIS, status of neutrophil count control, prophylactic administration status of G-CSF) occurring in Japanese patients in clinical practice will be collected/evaluated.

2) Survey items

Presence/absence of adverse events (see Table 1 and "1) Events subject to survey"), name of the adverse event, date of onset, CTCAE Grade* (worst grade and its date), seriousness and its reasons (see Table 2), change in dosage and administration of ADCETRIS and AVD (presence/absence and details), treatment for the event (presence/absence and details), outcome assessment date, outcome, causal relationship with ADCETRIS** (see Table 3), over-time related changes in laboratory tests (neutrophil count etc.).

If the outcome has been assessed to be not recovered/not resolved or unknown, follow-up surveillance should be conducted as far as possible.

* This should be assessed in accordance with the U.S. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

** If ADCETRIS is assessed to be not related, the rationale for assessment should be collected.

3) Survey period

Period from the start of ADCETRIS to 2 weeks after the completion of 12 doses or the discontinuation of ADCETRIS

Table 1 Definition of adverse events

An adverse event (AE) refers to any unfavorable medical event that has occurred to a patient administered with a drug. AEs do not necessarily refer to only events whose causal relationship with the administration of the drug is clear. In other words, AEs are any unfavorable events or unintended signs (including abnormalities in laboratory test results), or symptoms or diseases occurring when a drug is administered, in which presence/absence of the causal relationship with the drug administered does not matter.

Table 2 Assessment criteria for seriousness

1. Results in death (death) 2. Life-threatening (risk of death) "Life-threatening" refers to a case where a patient was at risk of death when the event occurred. It does not refer to any hypothetical situation that if the event had been more serious the patient would have died. 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization) 4. Results in persistent or significant disability/incapacity (disorder) 5. Congenital anomaly/birth defect (congenital anomaly) 6. Not immediately life-threatening or results in death or hospitalization but requires treatment to avoid consequences in the above 1 to 5, or endangers patients.

Table 3 Assessment criteria for the causal relationship between adverse events and ADCETRIS

Assessment	Assessment criteria
Related	An adverse event in which there is a temporal relationship with the drug (including the time lapse after the discontinuation) or whose causal relationship cannot be ruled out because there is at least a reasonable possibility that the drug is involved, despite other suspected factors such as underlying diseases, complications, concomitant drugs, and concomitant treatment.
Not related	An adverse event in which there is no temporal relationship with the drug or which can be very likely caused by other factors such as underlying diseases, complications, concomitant drugs, and concomitant treatment.

10.0 ANALYSIS ITEMS AND METHOD

10.1 ITEMS RELATED TO CASE STRUCTURE

The number of enrolled patients, number of patients whose survey sheets have been collected, number of cases subject to safety evaluation, number of cases subject to efficacy evaluation, number of patients excluded from evaluation, and reasons for exclusion should be aggregated.

10.2 PATIENT CHARACTERISTICS

Patient characteristics including the gender, age, duration of Hodgkin's lymphoma, lesion, and clinical stage should be aggregated.

10.3 TREATMENT

The administration status of ADCETRIS, administration status of AVD, and administration status of G-CSF, etc. should be aggregated.

10.4 ITEMS RELATED TO SAFETY

The following items should be aggregated in patients subject to safety evaluation. Adverse events should be rephrased using MedDRA/J and summarized in Preferred Term (PT) and System Organ Class (SOC).

10.4.1 INCIDENCE OF ADVERSE EVENTS

The frequencies of adverse events (neutropenia and febrile neutropenia) which occurred during the observation period should be aggregated according to the time of onset, severity (CTCAE grade), seriousness, and causal relationship with ADCETRIS.

10.4.2 FACTORS THAT MAY AFFECT THE SAFETY

The frequencies of adverse reactions (neutropenia and febrile neutropenia) which occurred during the observation period should be aggregated according to the classification, such as patient characteristic factors (gender, age, presence/absence of concurrent renal dysfunction, presence/absence of concurrent hepatic dysfunction, etc.) and the details of treatment (administration status of G-CSF, etc.).

10.5 ITEMS RELATED TO EFFICACY

The tumor response (best response) through the discontinuation or completion of ADCETRIS should be aggregated in patients subject to efficacy evaluation.

11.0 REGISTRATION OF SURVEY INFORMATION

Information about this survey should be registered to the following public website before the start of this survey:

- Japan Pharmaceutical Information Center- Clinical Trials Information:
  Japan Pharmaceutical Information Center-Clinical Trials Information
- U.S. National Institute of Health, clinical trial registration system: ClinicalTrials.gov

12.0 ORGANIZATIONAL STRUCTURE

12.1 SUPERVISOR

Takeda Pharmaceutical Company Limited

[redacted]

13.0 MEDICAL ADVISOR

[redacted]

14.0 CONTRACT RESEARCH ORGANIZATION

(1) [redacted]

Assignment:Registration center, data management operations, storage of records, medical writing, and support operations related to post-marketing surveys

(2) [redacted]

Assignment: Database construction

(3) [redacted]

Assignment: Statistical analysis

(4) [redacted]

Assignment: Monitoring

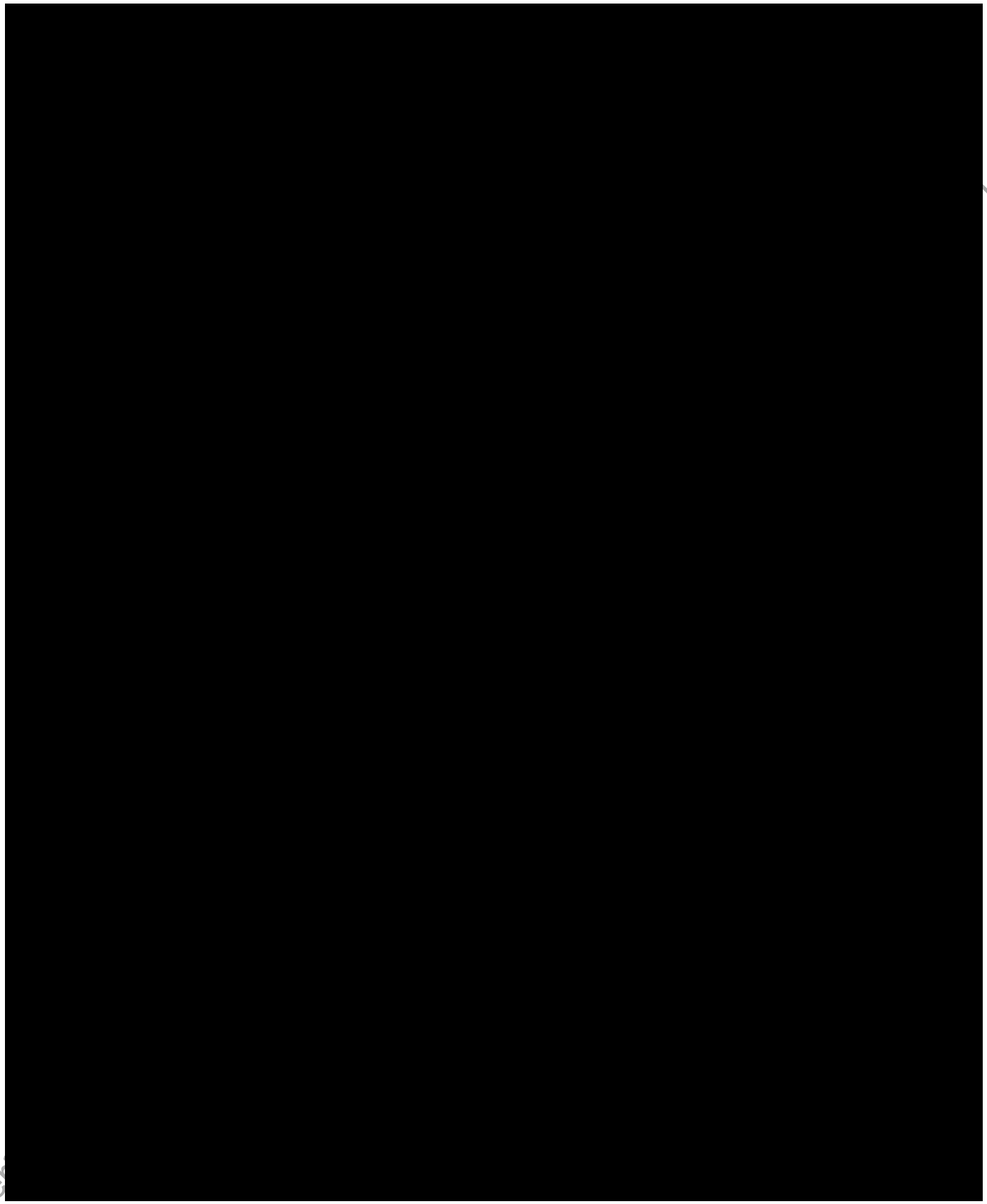
15.0 OTHER NECESSARY MATTERS

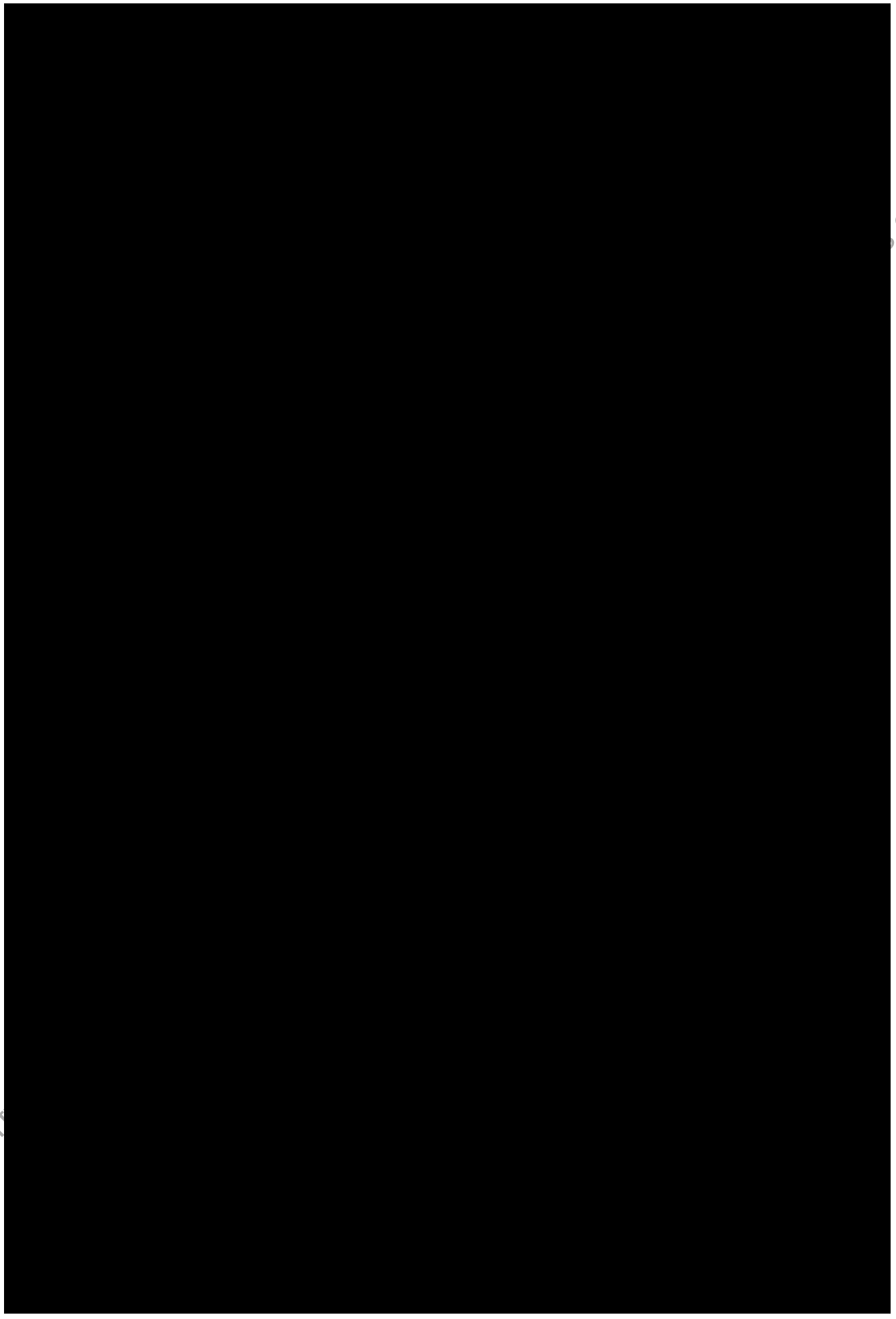
15.1 REVISION OF THE PROTOCOL

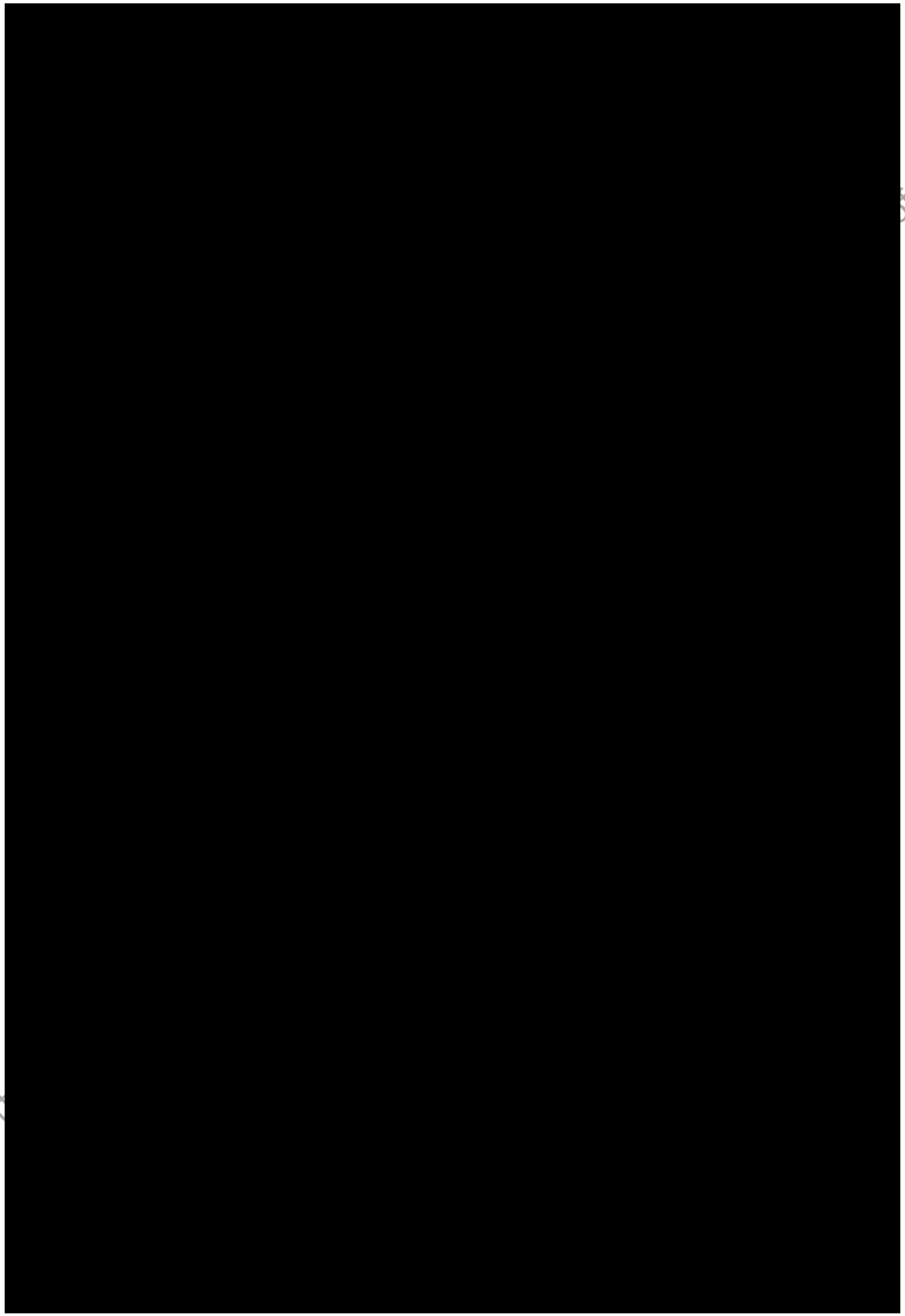
During the survey period, the progress of survey, occurrence of adverse reactions and serious adverse reactions that cannot be predicted from the Precautions, presence/absence of elevated frequency of specific adverse reactions, and appropriateness of survey items should be understood, and if necessary, this Protocol should be reviewed and revised. Additionally, approval for a partial change in the Dosage and Administration or Indications is obtained during the survey period, the necessity to revise this Protocol should be discussed and the Protocol should be revised, where necessary.

15.2 ACTIONS TO BE TAKEN IF PROBLEMS AND QUESTIONS ARISE

If any problem is found in the safety and efficacy, data should be reviewed to take actions.







Document History

Version	Date	Comments
original version	2018/10/22	New document
2nd version	2018/12/25	To add the period when patients could be registered
3rd version	2019/06/01	For minor changes in “13.0 CONTRACT RESEARCH ORGANIZATION”
4th version	2020/06/30	Because of the extension of the scheduled period of survey as well as addition and minor changes in “13.0 CONTRACT RESEARCH ORGANIZATION”
5th version	2021/01/15	For addition in “13.0 CONTRACT RESEARCH ORGANIZATION”
6th version	2022/05/11	For minor changes in “12.0 ORGANIZATIONAL STRUCTURE”
7th version	2023/04/06	For minor changes in “14.0 CONTRACT RESEARCH ORGANIZATION”
8th version	2023/09/12	In order to add the date of completion of the survey (date of completion of final analysis) to “8.0 SCHEDULED PERIOD OF SURVEY”