Statistical Analysis Plan

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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

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

Statistical Analysis Plan

（Final Analysis）

Product name : Adcetris for Intravenous Infusion 50 mg

Study title : General use-results surveillance
「Untreated CD30 positive Hodgkin's lymphoma」

Sponsor : Takeda Pharmaceutical Company Limited.

[redacted]

version 1.0 : January 26, 2023

目　次

1 Definitions of terms

1.1 List of Terms and Abbreviations

- This product：Adcetris for Intravenous Infusion 50 mg is abbreviated as Adcetris.
- Adverse events：adverse events that occurred after administration of Adcetris.
- Adverse reactions：Abbreviation for the term “adverse reactions/infections.” Adverse events assessed by the investigator as having a causal relationship with Adcetris other than "Not related". In this statistical analysis plan, the term "adverse drug reactions/infections" will be used in the title, and "adverse drug reactions" will be used in the text and tables.
- Serious adverse events: Adverse events assessed as "serious" by the investigator. Events listed in the MedDRA code list (PT code) using the Takeda Medically Significant AE List as the Important Medical Events List will be handled as serious events, even if the assessment by the investigator is “non-serious.
- Related to this product: An adverse event not related to Adcetris.
- Not related to this product: Adverse events assessed as not related to Adcetris.
- Summary statistics: A general term for number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Patients whose survey form was not collected: Patients whose survey form was not collected among registered patients.
- CRF collected patients: Patients whose CRF has been collected among registered patients.
- Days after treatment: Day -1 is defined as the day before the start of treatment with Adcetris, and Day 1 is defined as the day of the start of treatment with Adcetris.
- Duration of Adcetris treatment (days): End date of Adcetris treatment − start date of Adcetris treatment +1
- Timing of onset of adverse events (or adverse drug reactions, etc.): Calculated as the date of onset of adverse events (or adverse drug reactions, etc.) − the start date of the first dose of Adcetris +1.
- Time from diagnosis of Hodgkin's lymphoma to first dose of Adcetris:
    - Actual number (unit: months) = (Year of the first administration of Adcetris − Year of the diagnosis of Hodgkin's lymphoma) ×12+ (Month of the first administration of Adcetris − Month of the diagnosis of Hodgkin's lymphoma) If the month of the diagnosis is unknown, it should be calculated as January of the year described.

- Patients complicated with renal impairment: Patients for whom Takeda MedDRA query (Hereinafter referred to as TMQ) (Renal Disease) is entered in the disease name column.
- Patients complicated with hepatic impairment: Patients with a complication corresponding to MedDRA standard query (hereinafter referred to as SMQ) code 20000005 (liver disorder SMQ [scope: narrow]) described in the disease name column.
- BMI(kg/m^2): Calculated as weight (kg)/height $(m)^2$ (rounded off to the first decimal place).
- Treatment status
    - Early treatment: G-CSF formulations administered within 5 days of the first dose of Adcetris.
    - Non-early administration: Administration of G-CSF on or after Day 6 of the first administration of Adcetris.
    - No early administration: Cases without administration of G-CSF preparations and cases with administration only other than early administration.
- Approved dose of Adcetris: 1.2 mg/kg per dose.

1.2 Analysis Sets

The "safety evaluation population" and "efficacy evaluation population" will be set as the analysis sets for the general use-results survey. This analysis set is defined as follows:.

Safety analysis set

Defined as "Patients treated with Adcetris who had no major protocol violations and whose safety can be evaluated". Specifically, patients with locked CRFs who meet the following conditions will be excluded from the safety analysis set.

- Adcetris not administered
- Registration prior to the contract period
- Enrollment after Day 31 of Adcetris treatment
- Unknown adverse event
- Withdrawal of consent

Efficacy analysis set

In this statistical analysis plan, "Patients evaluable for efficacy with no major protocol violations among patients evaluable for safety" is defined as “patients included in efficacy evaluation.” Patients eligible for the safety evaluation who meet the following conditions will be excluded from the efficacy evaluation population.

- Non-target disease
- Inclusion criteria violation
- Violation of exclusion criteria

1.3 Number of digits to be displayed

- Percentage (%)
  Incidence of adverse events or adverse drug reactions:
  Round the second decimal place and display to the second decimal place.
  Other than the above:
  Round the second decimal place and display to the first decimal place.

- Summary statistics
  Mean, 1st quantiles, median, 3rd quantiles:
  The source data will be rounded to the first decimal place and displayed.

  Standard deviation:
  The data will be rounded to the second decimal place of the source data.
  Min, Max:
  The same number of digits as that of the source data will be displayed.

1.4 Important identified risks, important potential risks, and important missing information

- Important identified risks

  - Bone marrow depression: Events corresponding to MedDRA PT code 10029366 (neutrophil count decreased) or 10016288 (febrile neutropenia). Among events corresponding to bone marrow depression, Grade ≥ 3 adverse events were collected in this study.

2 Number of medical institutions surveyed and the number and composition of patients enrolled

2.1 Disposition of patients

Survey for analysis：General use-results survey

Subjects for analysis：All enrolled patients (patients enrolled)

Analysis item：
- Patients enrolled
- Study sites
- CRF not collected
- Case report forms collected
- Patients excluded from safety evaluation※
  - Reason for exclusion (duplicate counting) [Non-treatment with Adcetris, enrollment before the contract period, enrollment after the start date of treatment with Adcetris 31 days, unknown presence or absence of adverse events, withdrawal of consent]
- Safety analysis set
- Patients excluded from efficacy evaluation※
  - Reason for exclusion (duplicate counting) [Off-label use, violation of inclusion criteria, violation of exclusion criteria]
- Efficacy analysis set

Method of Analysis：For the above analytical variables, the following analyses will be performed to prepare a case composition diagram.

Also, the number of medical institutions surveyed will be shown for patients registered. A medical institution with a different department in the survey will be counted as 1 medical institution.

If there is no subject applicable to the reason for exclusion, 0 subject will be displayed.

For patients excluded from safety evaluation and patients excluded from efficacy evaluation, the number of patients by reason for exclusion will be tabulated and a list will be prepared.

*“Patients excluded from safety evaluation ” refer to patients excluded from“ patients included in safety evaluation ” among patients whose survey form was collected. Similarly, "patients excluded from efficacy evaluation" refers to

patients excluded from the "patients eligible for efficacy evaluation" among the "patients eligible for safety evaluation."

（1） Frequency tabulation

3 Patient characteristics

3.1 Patient characteristics

Analysis population：	Safety analysis population	
Analysis item：	Sex	[Male, female]
	Age (years)	［Min <= - < 18, 18 <= - < 30, 30 <= - < 40, 40 <= - < 50, 50 <= - < 60, 60 <= - < 70, 70 <= - < 80, 80 <= - <= Max］
	Time from diagnosis of Hodgkin's lymphoma to first dose of Adcetris (months)	[From the current month, the following month, and the second and subsequent months]
	Lesion site (multiple counting)	[Lymph nodes, spleen, liver, lung, bone, central nervous system, bone marrow, skin, others]
	Clinical Stage (Ann Arbor Classification)	[Stage I, II, III, IV, unknown]
	Presence or absence of B symptoms	[Absent, present]
	ECOG Performance Status	［0, 1, 2, 3, 4］
	Treatment category (at the start of treatment with Adcetris)	[Outpatient/inpatient]
	Complications	[Absent, present]
	Presence or absence of concomitant renal impairment	[Absent, present]
	Presence or absence of concomitant hepatic impairment	[Absent, present]
	Presence or absence of medical history	[Absent, present, unknown]
	Body weight (kg)	［Min <= - < 40.0, 40.0 <= - < 50.0, 50.0 <= - < 60.0, 60.0<= - < 70.0, 70.0 <= - <= Max, not measured］
	BMI（kg/m^2）	［Min <= - < 18.5, 18.5 <= - < 25.0, 25.0 <= - < 30.0, 30.0 <= - <= Max］
	Pregnancy	[Absent, present]
	Breastfeeding (females only)	[Absent, present]
Method of analysis：	For the above analytical variables, frequency tabulation of discrete data and summary statistics of continuous data will be calculated.	

4 Treatment

4.1 Administration status of Adcetris

Analysis population：	Safety analysis population	
Analysis item：	Adcetris initial dose (mg/kg)	［Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2, 1.2 < - <= Max］
	Mean dose of Adcetris per administration (mg/kg)	［Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2, 1.2 < - <= Max］
	Adcetris dose per 2 weeks (mg/kg/2 weeks)	［Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2, 1.2 < - <= Max］
	Maximum number of doses	[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12]
	Reasons for Discontinuation of Adcetris (Multiple Count)	［The treatment goal was achieved., Onset of Grade ≥ 3 "neutropenia" or "febrile neutropenia", The patient stopped visiting the hospital due to transfer, pregnancy, Due to lack of efficacy, Others
Method of Analysis：	For the above analytical variables, frequency tabulation of discrete data and summary statistics of continuous data will be calculated.	

4.2 AVD exposure

Analysis population：	Safety analysis population
Analysis item：	Initial dose of doxorubicin hydrochloride（mg/ m^2）
	Mean dose of doxorubicin hydrochloride per administration（mg/ m^2）
	Vinblastine sulfate initial dose（mg/ m^2）
	Mean dose of vinblastine sulfate per dose（mg/ m^2）
	Dacarbazine initial dose（mg/ m^2）
	Mean single dose of dacarbazine（mg/ m^2）
Method of Analysis：	Summary statistics of continuous data will be calculated for the above analytical variables.

4.3 Administration status of G-CSF preparations

Analysis population：	Safety analysis population	
Analysis item：	Presence/absence of administration of G-CSF preparations	[Absent, present]

	Treatment status	[With early administration, only administration other than early administration]
	Drug name	
Method of Analysis：	Frequencies of the above analytical variables will be tabulated.	

5 Safety analysis

5.1 Occurrence of adverse events, adverse drug reactions, and infections

5.1.1 Incidence of adverse events

Analysis population： Safety analysis population

Analysis item： Adverse events

Analytical method： For the above analytical variables, the following analyses should be performed.

（1） Number of patients with adverse events

（2） Number of adverse events

（3） Incidence of adverse events

（4） Type of adverse event

The method of accounting for each analysis is as follows.

【Number of patients with adverse events】

- Number of patients with adverse events.

【Number of adverse events】

- Number of adverse events experienced. If the same adverse event occurs more than once in the same patient, the total number of events will be tabulated.

【Incidence of adverse events】

- Calculate as the number of patients with adverse events/the number of patients evaluable for safety ×100.

【Type of adverse event】

- AEs will be coded using MedDRA/J. The data will be broadly classified by SOC and tabulated by PT. Note that cases in the SOC of “Investigations ” will be summarized by HLGT (HLGT codes are sorted in ascending order, but not output) and by PT.
- In the SOC, the number and percentage of patients with adverse events are presented in internationally agreed order of SOC.If the same SOC occurs more than once in the same subject, the subject will be counted as 1 subject in the SOC.
- For PTs, the number of patients with adverse events and the incidence will be presented in ascending order of PT codes.If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient for the PT.

5.1.2 Occurrence Status of Adverse Reactions/Infections

Analysis population： Safety analysis population

Analysis item： Adverse reactions

Analytical method： For the above analytical variables, the following analyses should be performed.

（1） Number of patients with adverse drug reactions
（2） Number of adverse drug reactions
（3） Incidence of adverse drug reactions
（4） Types of adverse drug reactions, etc.

The method of accounting for each analysis is as follows.

【Number of patients with adverse drug reactions】

- Number of patients with adverse drug reactions

【Number of adverse drug reactions】

- Number of adverse drug reactions. If the same adverse drug reaction, etc. occurs multiple times in the same patient, the total number of events will be tabulated.

【Incidence of ADRs】

- Calculate as the number of patients with adverse drug reactions/number of patients evaluable for safety ×100.

【Types of adverse reactions】

- Adverse drug reactions will be coded using MedDRA/J. The data will be broadly classified by SOC and tabulated by PT. Note that cases in the SOC of "Investigations " will be summarized by HLGT (HLGT codes are sorted in ascending order, but not output) and by PT.
- In the SOC, the number of patients with adverse drug reactions/infections and the incidence of them are described in internationally agreed order of SOC. If the same SOC occurs more than once in the same subject, the subject will be counted as 1 subject in the SOC.
- For PTs, the number of patients with adverse drug reactions/infections and the incidence of them will be described in ascending order of PT codes. If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient for the PT.

5.1.3 Adverse events, adverse reactions, and infections included in the safety specifications

5.1.3.1 Adverse events included in safety specifications

Analysis Safety analysis population

population：

Analysis item：	Adverse events included in safety specifications (important identified risks)
Stratification item：	Seriousness ［Serious, non-serious］
Method of Analysis：	For the above analysis set, analyses should be performed in the same manner as in Section 5.1.1 for each of the subgroups of stratification factors by risk. If the same SOC/PT occurs more than once in the same patient, the patient will be counted as 1 patient in the SOC/PT. However, if the seriousness is different, 1 case shall be counted for each of serious and non-serious cases. The risks covered should also follow the definition provided in the important identified risks.

5.1.3.2 Incident Status of Adverse Reactions/Infections Included in Safety Specifications

Analysis population：	Safety analysis population
Analysis item：	Adverse reactions corresponding to safety specifications (important identified risks)
Stratification item：	Seriousness ［Serious, non-serious］
Method of Analysis：	For the above analysis set, analyses should be performed in the same manner as in Section 5.1.2 for each of the subgroups of stratification factors by risk. If the same SOC/PT occurs more than once in the same patient, the patient will be counted as 1 patient in the SOC/PT. However, if the seriousness is different, 1 case shall be counted for each of serious and non-serious cases. The risks covered should also follow the definition provided in the important identified risks.

5.2 Occurrence status of adverse events, adverse reactions, and infections in patients excluded from safety evaluation

5.2.1 Adverse events in patients excluded from safety evaluation

Subjects analyzed：	Subjects excluded from safety evaluation
Analysis item：	Adverse events
Method of Analysis：	For the above analytical variable, analyses should be performed in the same manner as in Section 5.1.1.

5.2.2 Data on adverse reactions and infections in patients excluded from safety evaluation

Subjects analyzed：	Subjects excluded from safety evaluation
Analysis item：	Adverse reactions
Method of Analysis：	For the above analytical variable, analyses should be performed in the same manner as in Section 5.1.2.

5.3 Seriousness, CTCAE Grade (worst value), timing of onset, outcome, occurrence of adverse events and adverse drug reactions/infections by causal relationship with Adcetris

5.3.1 Seriousness, CTCAE Grade (worst value), timing of onset, outcome, occurrence of adverse events by causal relationship with Adcetris

Analysis population：	Safety analysis population	
Analysis item：	Adverse events	
Stratification item：	Total	
	Seriousness	［Serious, non-serious］
	CTCAE Grade(worst)	［Grade3, Grade4, Grade5］
	Time of onset (days)	［1 <= - <= 14, 15 <= - <= 28, 29 <= - <= 56, 57 <= - <= 112, 113 <= - <= Max］
	Time of onset (number of doses)	［After the first dose to before the second dose, after the second dose to before the third dose, after the third dose to before the fifth dose, after the fifth dose to before the ninth dose, and after the ninth dose］
	Outcome	［Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to the event), unknown］
	Relationship to Adcetris	［Related, not related］
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.1.1 for each of the subgroups of the stratification factors. If the same SOC/PT occurs more than once in the same patient, the patient will be counted as 1 patient in the SOC/PT. However, for the same SOC, one case will be adopted in the following order of priority, and the same PT will be adopted as	

one case for the content of any of the stratification items in the following order of priority.
Seriousness：serious → non-serious
CTCAE Grade (worst)：Grade5→Grade4→Grade3
Time of onset (days)：1 to 14 days →15 to 28 days →29 to 56 days →57 to 112 days → ≥ 113 days
Time of onset (number of doses)：After the first dose to before the second dose → After the second dose to before the third dose → After the third dose to before the fifth dose → After the fifth dose to before the ninth dose → After the ninth dose and thereafter
Outcome: death (due to the event) → recovered with sequelae → not recovered → recovering → recovered → unknown
Causal relationship with Adcetris: Related → Not related

5.3.2 Occurrence Status of Adverse Reactions/Infections by Seriousness, CTCAE Grade (Worst Value), Time of Onset, and Outcome

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item：	Total	
	Seriousness	［Serious, non-serious］
	CTCAE Grade (worst)	［Grade3, Grade4, Grade5］
	Time of onset (days)	［1 <= - <= 14, 15 <= - <= 28, 29 <= - <= 56, 57 <= - <= 112, 113 <= - <= Max］
	Time of onset (number of doses)	[After the first dose to before the second dose, after the second dose to before the third dose, after the third dose to before the fifth dose, after the fifth dose to before the ninth dose, and after the ninth dose]
	Outcome	[Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to the event), unknown]
Method of	For the above analysis sets, analyses should be performed in the same manner as	

Analysis： in Section 5.1.2 for each of the subgroups of the stratification factors.If the same SOC/PT occurs more than once in the same patient, the patient will be counted as 1 patient in the SOC/PT.However, for the same SOC, one case will be adopted in the following order of priority, and the same PT will be adopted as one case for the content of any of the stratification items in the following order of priority.

Seriousness: serious → non-serious

CTCAE Grade (worst value)：Grade5→Grade4→Grade3

Time of onset (days): 1 to 14 days →15 to 28 days →29 to 56 days →57 to 112 days → ≥ 113 days

Timing of onset (number of doses): After the first dose to before the second dose → After the second dose to before the third dose → After the third dose to before the fifth dose → After the fifth dose to before the ninth dose → After the ninth dose and thereafter

Outcome: death (due to the event) → recovered with sequelae → not recovered → recovering → recovered → unknown

5.4 Occurrence Status of Adverse Reactions/Infections by Patient Background and Treatment Factors

5.4.1 Occurrence status of adverse drug reactions/infections by patient background factor and treatment details factor

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item：	Sex	[Male, female]
	Age (years)	［Min <= - < 18, 18 <= - < 30, 30 <= - < 40, 40 <= - < 50, 50 <= - < 60, 60 <= - < 70, 70 <= - < 80, 80 <= - <= Max］
	Time from diagnosis of Hodgkin's lymphoma to first dose of Adcetris (months)	[From the current month, the following month, and the second and subsequent months]
	Lesion site (multiple counting)	[Lymph nodes, spleen, liver, lung, bone, central nervous system, bone marrow, skin, others]
	Clinical Stage (Ann Arbor	[Stage I, II, III, IV, unknown]

Classification)	
Presence or absence of B symptoms	[Absent, present]
ECOG Performance Status	［0, 1, 2, 3, 4］
Treatment classification (at the start of treatment with Adcetris)	[Outpatient/inpatient]
Presence or absence of complications	[Absent, present]
Presence or absence of concomitant renal impairment	[Absent, present]
Presence or absence of concomitant hepatic impairment	[Absent, present]
Presence or absence of medical history	[Absent, present, unknown]
Weight (kg)	［Min <= - < 40.0, 40.0 <= - < 50.0, 50.0 <= - < 60.0, 60.0<= - < 70.0, 70.0 <= - <= Max, Not measured］
BMI（kg/m^2）	［Min <= - < 18.5, 18.5 <= - < 25.0, 25.0 <= - < 30.0, 30.0 <= - <= Max］
Adcetris initial dose（mg/kg）	［Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2, 1.2 < - <= Max］
Mean dose of Adcetris per administration（mg/kg）	［Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2, 1.2 < - <= Max］
Adcetris dose per 2 weeks（mg/kg/2weeks）	［Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2, 1.2 < - <= Max］
G-CSF Early administration	[Absent, present]

Method of Analysis：

For the above analytical variable, the following analyses should be performed for each of the subgroups of the stratification factors.

Number of patients with adverse drug reactions

Incidence of adverse drug reactions

The method of accounting for each analysis is as follows.

【Number of patients with adverse drug reactions】

- Number of patients with adverse drug reactions

【Incidence of ADRs】

Calculate as the number of patients with adverse drug reactions/number of patients evaluable for safety ×100.

5.4.2 Occurrence Status of ADRs and Infections by Gender

Analysis　Safety analysis population

population：		
Analysis item：	Adverse reactions	
Stratification item：	Sex	[Male, female]
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.1.2 for each of the subgroups of the stratification factors.	

5.4.3 Occurrence Status of Adverse Reactions and Infections by Age Group

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item：	Age (years)	［Min <= - < 18, 18 <= - < 30, 30 <= - < 40, 40 <= - < 50, 50 <= - < 60, 60 <= - < 70, 70 <= - < 80, 80 <= - <= Max］
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.1.2 for each of the subgroups of the stratification factors.	

5.4.4 Occurrence Status of Adverse Reactions/Infections by Presence/Absence of Complication Renal Impairment

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item：	Presence or absence of concomitant renal impairment	[Absent, present]
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.1.2 for each of the subgroups of the stratification factors.	

5.4.5 Occurrence Status of Adverse Reactions/Infections by Presence/Absence of Complication of Hepatic Impairment

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item：	Presence or absence of concomitant hepatic impairment	[Absent, present]
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.1.2 for each of the subgroups of the stratification factors.	

5.4.6 Occurrence Status of Adverse Reactions/Infections by Presence/Absence of Early G-CSF Administration

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item：	Presence or absence of early G-CSF administration	[Absent, present]
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.1.2 for each of the subgroups of the stratification factors.	

5.4.7 Occurrence Status of Adverse Reactions/Infections by Presence/Absence of Early G-CSF Administration , Seriousness, CTCAE Grade (Worst Value), Time of Onset, and Outcome

5.4.7.1 Occurrence Status of Adverse Reactions/Infections by Presence/Absence of Early G-CSF Administration and by Seriousness

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item 1：	Presence/absence of early G-CSF administration	[Absent, present]
Stratification item 2：	Seriousness	[Serious, non-serious]
Method of analysis：	For the above analysis sets, the same analyses as those in Section 5.1.2 will be performed for each stratum of Stratification Item 2 after stratifying for Stratification Item 1. If the same SOC/PT occurs more than once in the same patient, the patient will be counted as 1 patient in the SOC/PT. However, for the same SOC, one case will be adopted in the following order of priority, and for the same PT, one case will be adopted for the content of any of the stratification items 2 in the following order of priority. Seriousness: serious → non-serious	

5.4.7.2 Occurrence Status of Adverse Reactions/Infections by Presence/Absence of Early G-CSF Administration and CTCAE Grade (Worst)

Analysis population：	Safety analysis population
Analysis item：	Adverse reactions

Stratification item 1：	Presence/absence of early G-CSF administration	[Absent, present]
Stratification item 2：	CTCAE Grade (worst)	［Grade3, Grade4, Grade5］
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.4.7.1.If the same SOC/PT occurs more than once in the same patient, the patient will be counted as 1 patient in the SOC/PT.However, for the same SOC, one case will be adopted in the following order of priority, and for the same PT, one case will be adopted for the content of any of the stratification items 2 in the following order of priority. CTCAE Grade (worst)：Grade5→Grade4→Grade3	

5.4.7.3 Occurrence Status of Adverse Reactions/Infections by Presence/Absence of Early G-CSF Administrationand Onset Time (Day)

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item 1：	Presence/absence of early G-CSF administration	[Absent, present]
Stratification item 2：	Time of onset (days)	［1 <= - <= 14, 15 <= - <= 28, 29 <= - <= 56, 57 <= - <= 112, 113 <= - <= Max］
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.4.7.1. If the same SOC/PT occurs more than once in the same patient, the patient will be counted as 1 patient in the SOC/PT.However, for the same SOC, one case will be adopted in the following order of priority, and for the same PT, one case will be adopted for the content of any of the stratification items 2 in the following order of priority. Time of onset (days): 1 to 14 days →15 to 28 days →29 to 56 days →57 to 112 days → ≥ 113 days	

5.4.7.4 Occurrence Status of Adverse Reactions/Infections by Presence/Absence of Early G-CSF Administration and Onset Time (Dose)

Analysis population：	Safety analysis population
Analysis item：	Adverse reactions

Stratification item 1：	Presence/absence of early G-CSF administration	[Absent, present]
Stratification item 2：	Time of onset (number of doses)	[After the first dose to before the second dose, after the second dose to before the third dose, after the third dose to before the fifth dose, after the fifth dose to before the ninth dose, and after the ninth dose]
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.4.7.1.If the same SOC/PT occurs more than once in the same patient, the patient will be counted as 1 patient in the SOC/PT.However, for the same SOC, one case will be adopted in the following order of priority, and for the same PT, one case will be adopted for the content of any of the stratification items 2 in the following order of priority.Timing of onset (number of doses): After the first dose to before the second dose → After the second dose to before the third dose → After the third dose to before the fifth dose → After the fifth dose to before the ninth dose → After the ninth dose and thereafter	

5.4.7.5 Occurrence Status of Adverse Reactions/Infections by Presence/Absence of Early G-CSF Administration and Outcome

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item 1：	Presence/absence of early G-CSF administration	[Absent, present]
Stratification item 2：	Outcome	[Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to the event), unknown]
Method of Analysis：	For the above analysis sets, analyses should be performed in the same manner as in Section 5.4.7.1.If the same SOC/PT occurs more than once in the same patient, the patient will be counted as 1 patient in the SOC/PT.However, for the same SOC, one case will be adopted in the following order of priority, and for the same PT, one case will be adopted for the content of any of the stratification	

items 2 in the following order of priority.
Outcome: death (due to the event) → recovered with sequelae → not recovered → recovering → recovered → unknown

5.5 Administration status of Adcetris and AVD by outcome at the onset of adverse drug reactions/infections

Analysis population：	Safety analysis population	
Analysis item：	Adverse reactions	
Stratification item 1：	Presence or absence of change due to this event	[Absent, present]
	Breakdown of changes	[Dose reduction, drug cessation [dose delay], discontinuation]
Stratification item 2：：	Outcome	[Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown]
	Total	
Method of Analysis：	The subjects in the above analysis will be stratified with Stratification Item 1 (this product), and the frequency of the number of adverse drug reactions/infections will be tabulated for each stratum in Stratification Item 2. The same tabulation will be performed for AVD (Doxorubicin hydrochloride, vinblastine sulfate, and dacarbazine).	

6 Efficacy analysis

6.1 Antitumor response after the end of frontline therapy

Analysis population：	Patients in the efficacy analysis population for whom antitumor response was assessed	
Analysis item：	Antitumor effect	[With PET assessment, without PET assessment, total]
Method of Analysis：	For each of the above analysis items, frequency of assessment results will be tabulated for patients in the efficacy evaluation set for whom antitumor response has been assessed to calculate the response rate. In addition, a band graph will be prepared for the above analysis results.This tabulation will be performed for the entire population and patients excluding those who received a dose exceeding the approved dose.	

6.2 Antitumor effect after the end of frontline therapy by patient background factor and treatment factor

Analysis population：	Patients in the efficacy analysis set for whom antitumor response was assessed	
Analysis item：	Antitumor effect	[With PET assessment, without PET assessment, total]
Stratification item：	Sex	[Male, female]
	Age (years)	［Min <= - < 18, 18 <= - < 30, 30 <= - < 40, 40 <= - < 50, 50 <= - < 60, 60 <= - < 70, 70 <= - < 80, 80 <= - <= Max］
	Time from diagnosis of Hodgkin's lymphoma to first dose of Adcetris (months)	[From the current month, the following month, and the second and subsequent months]
	Lesion site (multiple counting)	[Lymph nodes, spleen, liver, lung,bone,central nervous system, bone marrow, skin, others]
	Clinical Stage (Ann Arbor Classification)	[Stage I, II, III, IV, unknown]
	Presence or absence of B symptoms	[Absent, present]
	ECOG Performance Status	［0, 1, 2, 3, 4］
	Treatment classification (at the start of treatment with Adcetris)	[Outpatient/inpatient]

Presence or absence of complications	[Absent, present]
Presence or absence of concomitant renal impairment	[Absent, present]
Presence or absence of concomitant hepatic impairment	[Absent, present]
Presence or absence of medical history	[Absent, present, unknown]
Body weight（kg）	［Min <= - < 40.0, 40.0 <= - < 50.0, 50.0 <= - < 60.0, 60.0<= - < 70.0, 70.0 <= - <= Max, Not measured］
BMI（kg/m^2）	［Min <= - < 18.5, 18.5 <= - < 25.0, 25.0 <= - < 30.0, 30.0 <= - <= Max］
Adcetris initial dose（mg/kg）	［Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2, 1.2 < - <= Max］
mean dose of Adcetris per administration （mg/kg）	［Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2, 1.2 < - <= Max］
Adcetris dose per 2 weeks （mg/kg/2weeks）	［Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2, 1.2 < - <= Max］
Presence or absence of early G-CSF administration	[Absent, present]

Method of Analysis：

For each of the above analysis items, the frequency of assessment results will be tabulated by stratum of the stratification items for patients who have been assessed for antitumor effect among the patients evaluable for efficacy, and the response rate will be calculated. This tabulation will be performed for the entire population and patients excluding those who received a dose exceeding the approved dose.

7 Adverse reactions and infections in the additional pharmacovigilance plan

7.1 Adverse reactions and infections included under the additional pharmacovigilance plan (Attached Form 12)

Analysis population：	Safety analysis population
Analysis item：	Adverse reactions corresponding to safety specifications (important identified risks)
Stratification item：	Seriousness [Serious, non-serious]
Analytical method：	For the above analytical variable, the following analyses should be performed for each of the subgroups of the stratification factors, in accordance with (Note) 1~4 of Form 12 in the Attachment of PSEHB/PED Notification No. 0325 No. 10 dated March 25, 2020. （1） Number of subjects with events and the incidence of them The order of description of the risk name and risk name shall be in accordance with the definition described in Important Identified Risks.

8 Case summary in post-marketing surveillance

8.1 Case summary in post-marketing surveillance (Attached form 16)

Subjects to be analyzed：	CRF collected cases
Analysis item：	Case No. Name of medical institution Sex Age Reason for use (Disease code, disease name) Concomitant conditions (Disease code, disease name) Route of administration Maximum dose Mean dose Unit Duration of use (duration of treatment with Adcetris) Concomitant medicinal products (Drug Code, Drug Name) Degree of effect Adverse Reactions (Disease code, disease name, and outcome) CRF number withdrawal Reason for withdrawal G-CSF Early administration of drug product
Analytical method：	For the above analysis items, a list will be prepared in accordance with the Guidelines for Preparation of the Reexamination Data Entry File issued by PSEHB/PED Notification No. 1119 No. 3 dated November 19, 2020.

Preparation history (version control)

version	date	Author/reviewer	comment
Version 1.0	2023.01.26	[redacted]	Preparation of the first version

Statistical Analysis Plan

(final analysis additional analysis)

LORO	Eye	Name	Adcetris for Intravenous Drip Infusion 50 mg
Dose	Inspection Name		General use-results survey "Previously untreated CD30 positive Hodgkin's lymphoma"
Sponsor			Takeda Pharmaceutical Company Limited.

[redacted]

Original: Prepared on September 7, 2023

TABLE OF CONTENTS

1 Definition of Terms, etc.

1.1 List of Terms and Abbreviations

•this drug: Adcetris for Intravenous Drip Infusion 50 mg is abbreviated as this drug.

•Adverse Event: AE occurred after administration of this drug.

•Adverse reactions, etc.: An abbreviation of the term “adverse reactions • infections.” Adverse events that are not "not related" to this drug as assessed by the managing physician. In this statistical analysis plan, the title is
“Adverse reactions • infections ” will be used, and“ adverse reactions, etc. ” will be used in the text and tables.

•Serious adverse events: Adverse events assessed as "serious" by the investigator. Takeda
The Important Medical Events List is used as the Medically Significant AE List, and events listed in the MedDRA code list (PT code) are handled as serious even if the investigator's assessment is “non-serious.”

•Related to this drug: An AE that is not related to this drug.

- Not related to this drug: An AE that is not related to this drug.

•Summary statistics: A collective term for sample size, mean, standard deviation, maximum, minimum, and quartiles.

•Patients whose CRFs were not collected: Registered patients whose CRFs were not collected.

•Patients whose CRFs were collected: Registered patients whose CRFs were collected.

•Days after administration: Day -1 is defined as the day before the start date of this drug treatment and Day 1 is defined as the start date of this drug treatment.

•Duration of treatment with this drug (days): end date of treatment with this drug (day): start date of treatment with this drug +1

•Timing of onset of an adverse event (or adverse drug reaction, etc.): The date of onset of the adverse event (or adverse drug reaction, etc.) will be calculated as the start date of the first administration of one drug +1.

•Time from Hodgkin's lymphoma diagnosis to first dose of this drug:

•Actual number (months) = (Year of the first administration of this drug - Year of the diagnosis of Hodgkin's lymphoma) X12+ (Month of the first administration of this drug - Month of the diagnosis of Hodgkin's lymphoma) If the month of the diagnosis is unknown, January of the year will be used for calculation.

•Patients complicated with renal impairment: Takeda MedDRA query (Hereinafter referred to as TMQ) in the field of disease name (Renal Complications applicable to “Disease ” are listed.

•Patients complicated with hepatic impairment: Patients in whom a complication corresponding to MedDRA standard query (Hereinafter referred to as SMQ) code 20000005 (liver disorder SMQ [scope: narrow]) is entered in the disease name field.

- BMI (kg/m ^{2}): Calculated as weight (kg)/height (m) ^{2} (rounded to the first decimal place).

•Administration status

- Early dose: G-CSF is administered within 5 days of the first dose of this drug.
- Non-early dose: G-CSF is administered on or after Day 6 of the first dose of this drug.
- No early administration: Patients without G-CSF preparation and patients receiving only non-early administration.
- Prophylactic administration: Patients who have received a G-CSF preparation by 14 days after the start of this drug and have not experienced an AE by the time of the first administration of G-CSF preparation. However, if the start date of an AE and the date of administration of a G-CSF preparation are the same, they are not included in the prophylactic administration.
- Administration other than prophylactic administration: The first dose of G-CSF preparation was administered more than 15 days after the start of this drug administration or after the onset of an AE.
- No prophylactic administration: Patients without G-CSF preparation and patients receiving only non-prophylactic administration.
- Timing of prophylactic administration: Day 1 of starting administration of G-CSF preparations Day 1 of starting administration of this drug +1 However, G-CSF preparations should be administered from the first dose of this drug to before the second dose.

•Approved dose of this drug: 1.2 mg/kg per dose.

1.2 Populations for Analyses

As the analysis population of the general drug use-results survey, the "subjects for safety evaluation" and the "subjects for efficacy evaluation" will be defined. This analysis set will be defined as follows:.

Subjects evaluable for safety

Defined as "Patients receiving this drug who had no major protocol violations and whose safety could be evaluated." Specifically, patients with locked CRFs who meet any of the following criteria will be excluded from the safety analysis set.

- this drug naïve
- Registration before the contract period
- Enrollment on or after Day 31 of this drug treatment
- Presence/absence of adverse event unknown
- Withdrawal of consent

Patients eligible for efficacy evaluation
In this statistical analysis plan, the "Patients evaluable for efficacy with no major protocol deviations among patients evaluated for safety" will be defined as the patients evaluated for efficacy. Patients who meet the following conditions among the patients evaluated for safety will be excluded from the patients evaluated for efficacy.

- Other than target disease
- Inclusion criteria violation
- Exclusion criteria violation

1.3 digits to be displayed

•Percentage (%)

Incidence of adverse events or adverse drug reactions:

Round and display to 2 decimal places.

Other than the above:

Round off to one decimal place.

•Summary statistics

Mean, 14 percentile, median, 34 percentile:

Rounded to one digit below the source data.

Standard deviation:

Round off to the second digit below the source data.

Min, Max:

Display the same number of digits as displayed in the source data.

1.4 Important identified risks, important potential risks, and important missing information

•Important identified risks

- •Bone marrow depression: Events corresponding to MedDRA PT codes 10029366 (neutrophil count decreased) and 10016288 (febrile neutropenia). The events collected in this survey were Grade ≥ 3 adverse events corresponding to bone marrow depression.

(2) Patient characteristics

2.1 Patient characteristics by early use or prophylactic use of G-CSF preparations

Analysis population:	Subjects evaluable for safety	
Analysis item: Sex		[Male, female]
	Age (years)	[Min <=- < 18,18 <= - < 30, 30 <=-< 40, 40 <= - < 50, 50 <= - < 60, 60<=-< 70, 70 <= - < 80, 80 <=- <=Max]
		[Min <= - < 65, 65 <= - <= Max][From the current month, the following month, and the month after next]
	Time from diagnosis of Hodgkin's lymphoma to first dose of this drug (months)	[Lymph nodes, spleen, liver, lung, bone, CNS, bone marrow, skin, others]
	Disease site (multiple counting)	[Oral stage, stage B, stage B, stage B unknown]
		[Absent, present]
	Clinical stage (Ann Arbor staging)	[0,1,2, 3, 4]
	Presence or absence of B symptoms	[Outpatient/inpatient]
	ECOG Performance Status	Absent, Present] Absent, Present] Absent, Present] Absent]
	Treatment category (at the start of this drug treatment)	[Absent, present, unknown]
	Complications	[Min <= - < 40.0, 40.0 <= - < 50.0,50.0 <= - < 60.0, 60.0<= - < 70.0,70.0 <= - <= Max, not measured]
	Presence or absence of concurrent renal impairment	[Min <=- < 18.5, 18.5 <= - < 25.0,25.0 <= - < 30.0, 30.0 <=- <=Max]
	Presence or absence of concurrent hepatic impairment	Absent, Present]
	Presence or absence of medical history	Absent, Present] Absent, Present] Absent, Present] Absent]
	Weight (kg)	
	BMI(kg/m2)	
	Pregnancy (females only)	
	Breastfeeding status (females only)	
Stratification item:	Presence or absence of early administration of G-CSF preparations	
	Presence or absence of prophylactic administration of G-CSF preparations	
Analytical method:	For the above analytical variables, in each of the subgroups of stratification factors (early administration of G-CSF preparations	
	Frequency tabulation of discrete data and summary statistics of continuous data will be calculated by the presence or absence of and the presence or absence of prophylactic administration of G-CSF preparations.	

(3) Matters related to safety

3.1 Occurrence status of adverse reactions/infections

3.1.1 Occurrence Status of Adverse Reactions • Infections by Presence or Absence of Early Administration or Prophylactic Administration of G-CSF Preparations (e.g., Adverse Reactions that Occurred within 14 Days after the Start of this drug Treatment)

Analysis population: Subjects evaluable for safety

Analysis item: Adverse reactions, etc. that occurred within 14 days after the start of administration of this drug

Stratification item: Presence or absence of early administration of G-CSF preparations [Absent, present]
Presence or absence of prophylactic administration of G-CSF preparations [Absent, present]

Analytical method: The above analysis items were analyzed by the presence or absence of early administration of G-CSF preparations and by the presence or absence of early administration of G-CSF preparations.

The following analyses will be performed by the presence or absence of prophylactic administration of the drug product.

(1) Number of patients with adverse drug reactions, etc. that occurred by 14 days after the start of administration of this drug

(2) Number of adverse drug reactions, etc. that occurred by 14 days after the start of administration of this drug

(3) Incidence of adverse drug reactions, etc. that occurred within 14 days after the start of administration of this drug

(4) Types of adverse drug reactions, etc. that occurred within 14 days after the start of administration of this drug

The calculation method for each analysis is as follows.
[Number of patients with adverse reactions, etc.]

- Number of patients with adverse reactions, etc. [Number of adverse reactions]
- Number of adverse drug reactions, etc. that occurred. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse reactions, etc.]

- Calculate with the number of patients with adverse drug reactions/number of patients evaluated for safety X100. [Types of adverse reactions]
- Adverse drug reactions will be coded using MedDRA/J. It will be roughly classified by SOC and tabulated by PT. SOC of "investigations" will be summarized by HLGT (Sort in ascending order of HLGT code, but do not output) and PT.
- In SOC, the number of patients with adverse drug reactions, etc. and the incidence will be described in SOC internationally agreed order. A subject with multiple occurrences of an event within an SOC should be counted only once for that SOC.
- By PT, the number of patients with adverse drug reactions, etc. and the incidence will be described in ascending order of PT codes. A subject who experienced the same PT more than once should be counted as 1 subject with the PT.

3.2 Occurrence Status of Adverse Reactions/Infections by Patient Background and Treatment Factor

3.2. 1 Occurrence of adverse drug reactions/infections by patient background factor and treatment factor (e.g., adverse drug reactions that occurred within 14 days after the start of administration of this drug)

Analysis population:	Subjects evaluable for safety	
Analysis item:	Adverse reactions, etc. that occurred within 14 days after the start of administration of this drug	
Stratification item:	Sex	[Male, female]
	Age (years)	[Min <=- < 18,18 <= - < 30, 30 <=- < 40, 40 <= - < 50, 50 <= - < 60, 60<=-< 70, 70 <= - < 80, 80 <=- <=Max]
	Time from diagnosis of Hodgkin's lymphoma to first dose of this drug (months)	[Min <= - < 65, 65 <= - <= Max][From the current month, the following month, and the month after next]
	Disease site (multiple counting)	[Lymph nodes, spleen, liver, lung, bone, CNS, bone marrow, skin, others]
	Clinical stage (Ann Arbor staging)	[Oral stage, stage B, stage B, stage B unknown]
	Presence or absence of B symptoms	[Absent, present]
	ECOG Performance Status	[0,1,2, 3, 4]
	Treatment category (at the start of this drug treatment)	[Outpatient/inpatient]
	Complications	[Absent, present]
	Presence or absence of concurrent renal impairment	[Absent, present]
	Presence or absence of concurrent hepatic impairment	Absent, Present]
	Presence or absence of medical history	Absent, present, unknown]
	Weight (kg)	[Min <= - < 40.0, 40.0 <= - < 50.0,50.0 <= - < 60.0, 60.0<= - < 70.0,70.0 <= - <= Max, not measured]
	BMI (kg/m2)	[Min <=- < 18.5, 18.5 <= - < 25.0,25.0 <= - < 30.0, 30.0 <=- <=Max]
	This drug loading dose (mg/kg)	[Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2,1.2 < - <= Max]
	Mean dose of this drug per administration (mg/kg)	[Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2,1.2 < - <= Max]
	This drug dose per 2 weeks (mg/kg/2 weeks)	[Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2,1.2 < - <= Max]
	Presence or absence of early administration of G-CSF preparations	Absent, Present]

Analytical method: For the above analytical variable, the following analyses should be performed for each stratum of the stratification factor.

Number of patients with adverse drug reactions, etc. that occurred by 14 days after the start of administration of this drug

Incidence of adverse drug reactions, etc. that occurred by 14 days after the start of administration of this drug The method of counting in each analysis is as follows.

[Number of patients with adverse reactions, etc.]

- Number of patients with adverse reactions, etc. [Incidence of adverse reactions, etc.]

Calculate with the number of patients with adverse drug reactions/number of patients evaluated for safety X100.

3.2. 2 Occurrence status of ADRs • Infections by sex (ADRs that occurred within 14 days after the start of administration of this drug, etc.)

Analysis population: Subjects evaluable for safety

Analysis item: Adverse reactions, etc. that occurred within 14 days after the start of administration of this drug

Stratification item: Sex [Male, female]

Analytical method: For the above analysis set, the following analyses will be performed for each stratum of the stratification factor.

Number of patients with adverse drug reactions, etc. that occurred by 14 days after the start of administration of this drug

Number of adverse drug reactions, etc. that occurred by 14 days after the start of administration of this drug

Incidence of adverse drug reactions, etc. that occurred within 14 days after the start of administration of this drug

Type of adverse drug reactions, etc. that occurred by 14 days after the start of administration of this drug The method of counting in each analysis is as follows.

[Number of patients with adverse reactions, etc.]

- Number of patients with adverse reactions, etc. [Number of adverse reactions]
- Number of adverse drug reactions, etc. that occurred. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse reactions, etc.]

- Calculate with the number of patients with adverse drug reactions/number of patients evaluated for safety X100. [Types of adverse reactions, etc.]
- Adverse drug reactions will be coded using MedDRA/J. It will be roughly classified by SOC and tabulated by PT. SOC of "investigations" will be summarized by HLGT (Sort in ascending order of HLGT code, but do not output) and PT.
- In SOC, the number of patients with adverse drug reactions, etc. and the incidence will be described in SOC internationally agreed order. A subject with multiple occurrences of an event within an SOC should be counted only once for that SOC.

By PT, the number of patients with adverse drug reactions, etc. and the incidence will be described in ascending order of PT codes. A subject who experienced the same PT more than once should be counted as 1 subject with the PT.

323 Onset status of ADRs • infections by age group (ADRs, etc. that occurred within 14 days after the start of administration of this drug)

Analysis population: Subjects evaluable for safety

Analysis item: Adverse reactions, etc. that occurred within 14 days after the start of administration of this drug

Stratification item: Age (years) [Min <=- < 18,18 <= - < 30, 30 <=- < 40, 40 <= - < 50, 50 <= - < 60, 60 <=-< 70, 70 <= - < 80, 80 <=- <=Max]
[Min <= - < 65, 65 <= - <= Max]

Analytical method: For the above analytical variable, the same analyses as those described in Section 3.2.2 were performed for each stratum of the stratification factor.

Perform.

3.2. 4 Incidence of ADRs • Infections by presence or absence of concurrent renal impairment (ADRs, etc. that occurred within 14 days after the start of administration of this drug)

Analysis population: Subjects evaluable for safety

Analysis item: Adverse reactions, etc. that occurred within 14 days after the start of administration of this drug

Stratification item: Presence or absence of concurrent renal impairment [Absent, present]

Analytical method: For the above analysis set, the same analyses as those described in Section 3.2.2 were performed for each stratum of the stratification factor.

Perform.

3. 2.5 Occurrence status of ADRs • Infections by presence or absence of concurrent hepatic impairment (ADRs, etc. that occurred within 14 days after the start of administration of this drug)

Analysis population: Subjects evaluable for safety

Analysis item: Adverse reactions, etc. that occurred within 14 days after the start of administration of this drug

Stratification item: Presence or absence of concurrent hepatic impairment [Absent, present]

Analytical method: For the above analysis set, the same analyses as those described in Section 3.2.2 were performed for each stratum of the stratification factor.

Perform.

3.3 Occurrence Status of Adverse Reactions • Infections by Seriousness, CTCAE Grade (Worst Value), and Outcome (Adverse Reactions, etc. that Occurred within 14 Days after the Start of this drug Treatment) Analysis Set: Subjects evaluable for safety

Analysis item: Adverse reactions, etc. that occurred within 14 days after the start of administration of this drug

Stratification item: Total

Seriousness	[Serious, non-serious]
CTCAE Grade (worst value)	[Grade3, Grade4, Grade5]
Outcome	[recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved but later]

Presence of residual disease, death (due to this event), unknown] Analysis method: In the above analysis population, subjects with or without early administration of G-CSF preparations and subjects with G-CSF

For each of the stratification factors with or without prophylactic administration of the product, the same analyses as those in Section 3.1.1 will be performed. A subject who experienced the same SOC/PT more than once should be counted as 1 subject in the SOC/PT. However, 1 subject within the same SOC will be included in the study according to the following order of priority, and 1 subject within the same PT will be included in the study according to the following order of priority for any of the stratification factors.

Seriousness: Serious - Non-serious

CTCAE Grade (worst value): Grade5—Grade4—Grade3

Outcome: Death (due to this event) Recovered once with sequelae 1 Not recovered/Not resolved T Recovering/Resolving T Unknown

[4] Re-output of the final analysis figures/tables (replacement)

4.1 Patient characteristics

Analysis population:	Subjects evaluable for safety	
Analysis item: Sex		
	Age (years)	[Male, female]
		[Min <=- < 18,18 <= - < 30, 30 <=- < 40, 40 <= - < 50, 50 <= - < 60, 60 <=-< 70, 70 <= - < 80, 80 <=- <=Max]
	Time from diagnosis of Hodgkin's lymphoma to first dose of this drug (months)	[From the current month, the following month and the month after next]
	Disease site (multiple counting)	[Lymph nodes, spleen, liver, lung, bone, CNS, bone marrow, skin, others]
	Clinical stage (Ann Arbor staging)	[Oral stage, stage B, stage B, stage B unknown]
	Presence or absence of B symptoms	[Absent, present]
	ECOG Performance Status	[0,1,2, 3, 4]
	Treatment category (at the start of this drug treatment)	[Outpatient/inpatient]
	Complications	[Absent, present]
	Presence or absence of concurrent renal impairment	[Absent, present]
	Presence or absence of concurrent hepatic impairment	[Absent, present]
	Presence or absence of medical history	Absent, present, unknown]
	Weight (kg)	[Min <= - < 40.0, 40.0 <= - < 50.0,50.0 <= - < 60.0, 60.0<= - < 70.0,70.0 <= - <= Max, not measured]
	BMI(kg/m2)	[Min <=- < 18.5, 18.5 <= - < 25.0,25.0 <= - < 30.0, 30.0 <=- <=Max]
	Pregnancy (females only)	Absent, Present]
	Breastfeeding status (females only)	Absent, Present]
Analysis Methods:	For the above analytical variables, frequency tabulation of discrete data and continuous data	
	Summary statistics will be calculated.	

4.2 Occurrence Status of Adverse Drug Reactions/Infections by Patient Background Factor and Treatment Factor

Analysis population:	Subjects evaluable for safety	
Analysis item: Adverse reactions, etc.		
Stratification item: Sex		[Male, female]
	Age (years)	[Min <=- < 18,18 <= - < 30, 30 <=- < 40, 40 <= - < 50, 50 <= - < 60, 60

	<=-< 70, 70 <= - < 80, 80 <=- <=Max]
	[From the current month, the following month, and the month after next]
Time from diagnosis of Hodgkin's lymphoma to first dose of this drug (months)	
Disease site (multiple counting)	[Lymph nodes, spleen, liver, lung, bone, CNS, bone marrow, skin, others]
Clinical stage (Ann Arbor staging)	stage B, stage B, stage B, stage B, unknown
Presence or absence of B symptoms	[Absent, present]
ECOG Performance Status	[0,1,2, 3, 4]
Treatment category (at the start of this drug treatment)	[Outpatient/inpatient]
Complications	Absent, Present]
Presence or absence of concurrent renal impairment	Absent, Present]
Presence or absence of concurrent hepatic impairment	Absent, Present]
Presence or absence of medical history	[Absent, present, unknown]
Weight (kg)	[Min <= - < 40.0, 40.0 <= - < 50.0,50.0 <= - < 60.0, 60.0<= - < 70.0,70.0 <= - <= Max, not measured]
BMI(kg/m2)	[Min <=- < 18.5, 18.5 <=- < 25.0,25. <= - < 30.0, 30. <= - <=Max]
This drug loading dose (mg/kg)	[Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2,1.2 < - <= Max]
Mean dose of this drug per administration (mg/kg)	Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2,1.2 < - <= Max]
This drug dose per 2 weeks (mg/kg/2 weeks)	Min <= - < 0.6, 0.6 <= - < 0.9, 0.9 <= - < 1.2, 1.2,1.2 < - <= Max]
Presence or absence of early administration of G-CSF preparations	Absent, Present]

Analytical method: For the above analytical variable, the following analyses should be performed for each stratum of the stratification factor.

Number of patients with adverse reactions, etc.

Incidence of adverse drug reactions

The calculation method for each analysis is as follows.

[Number of patients with adverse reactions, etc.]

•Number of patients with adverse reactions, etc.

[Incidence of adverse reactions, etc.]

Calculate with the number of patients with adverse drug reactions/number of patients evaluated for safety X100.

4.3 Antitumor effect after the end of frontline therapy by patient demographics and treatment factors

Analysis population: Patients whose antitumor effect was assessed among the patients evaluated for efficacy

Analysis item: Antitumor effect	[With PET assessment, without PET assessment, total]
Stratification item: Sex	[Male, female]
Age (years)	[Mln v=- < 18,18 v= - < 30, 30 v= < 40, 40 v= - v 50, 50 v= - v 60, 60 v= - v 70, 70 v= - v 80, 80 v= - v= Max]
Time from diagnosis of Hodgkin's lymphoma to first dose of this drug (months)	[From the current month, the following month, and the month after next]
Disease site (multiple counting)	[Lymph nodes, spleen, liver, lung, bone, CNS, bone marrow, skin, others]
Clinical stage (Ann Arbor staging)	[Oral stage, stage B, stage B unknown]
Presence or absence of B symptoms	Absent, Present]
ECOG Performance Status	[0,1,2, 3, 4]
Treatment category (at the start of this drug treatment)	[Outpatient/inpatient]
Complications	Absent, Present]
Presence or absence of concurrent renal impairment	Absent, Present]
Presence or absence of concurrent hepatic impairment	Absent, Present]
Presence or absence of medical history	[Absent, present, unknown]
Weight (kg)	[Min v= - v 40.0, 40.0 v= - v 50.0, 50.0 v= - v 60.0, 60.0v= - v 70.0, 70.0 v= -v= Max, not measured
BMI (kg/m2)	[Min v= - v 18.5, 18.5 v= - v 25.0, 25.。 v= -v 30.0, 30. v= - v=Max]
This drug loading dose (mg/kg)	[Min v= - v 0.6, 0.6 v= - v 0.9, 0.9 v=-v 1.2, 1.2,1.2 v - v= Max]
Mean dose of this drug per administration (mg/kg)	Min v= - v 0.6, 0.6 v= - v 0.9, 0.9 v= -v 1.2, 1.2,1.2 v - v= Max]
This drug dose per 2 weeks (mg/kg/2 weeks)	Min v= - v 0.6, 0.6 v= - v 0.9, 0.9 v= -v 1.2, 1.2,1.2 v - v= Max]
Presence or absence of early administration of G-CSF preparations	Absent, Present]

Analytical method: For each of the above analysis items, the tumor response was assessed in the efficacy analysis set.

Frequency tabulation of assessment results by stratum of stratification items in patients who were assessed

will be performed to calculate the response rate. This tabulation will be performed for the overall population and the patients excluding the patients who exceeded the approved dose.

Preparation history (version control)

Version	Date	Author/Reporter	Comments
Original Version	2023.9.7	[redacted]	Preparation of initial version [4] Regarding the re-output (replacement) of the final analysis figures and tables, there was an error in the derivation method for the "period category from the diagnosis of Hodgkin's lymphoma to the first dose of this drug" at the final analysis. Therefore, correction of the derivation method and re-output of related figures and tables were planned.