Official Title: A Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Axatilimab Monotherapy in Japanese Participants With Recurrent or Refractory Active Chronic Graft-Versus-Host Disease After at Least 2 Lines of Systemic Therapy

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Statistical Analysis Plan

INCA 34176-358

A Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Axatilimab Monotherapy in Japanese Participants With Recurrent or Refractory Active Chronic Graft-Versus-Host Disease After at Least 2 Lines of Systemic Therapy

Sponsor:	**Incyte Biosciences Japan GK** **Tokyo Midtown Hibiya 12F** **1-1-2 Yurakucho Chiyoda-ku, Tokyo 100-0006**
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SAP Author:	[redacted] [redacted]**, Biostatistics**
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This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAP	bone-specific alkaline phosphatase
BMI	body mass index
CD	cluster of differentiation
cGVHD	chronic graft-versus-host disease
CI	confidence interval
CR	complete response
CRF	Case Report Form
CSF-1	colony-stimulating factor 1
CTCAE	Common Terminology Criteria for Adverse Events
CTX	carboxy-terminal collagen crosslinks
DILI	drug-induced liver injury
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
FAS	Full Analysis Set
GI	gastrointestinal
HR	heart rate
IL	interleukin
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
mLSS	modified Lee Symptom Scale
NCI	National Cancer Institute
NIH	National Institutes of Health
NK	natural killer
ORR	overall response rate
PK	pharmacokinetic(s)
PO	oral(ly)
PR	partial response
PT	preferred term

Abbreviation	Term
QTc	QT interval corrected
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
QxW	every x weeks
SAP	Statistical Analysis Plan
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 3, open-label, multicenter study to evaluate the efficacy and safety of axatilimab in Japanese participants with recurrent or refractory active cGVHD who have received at least 2 prior lines of systemic therapy and discontinued due to progression of disease, intolerability, or toxicity.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCA 34176-358 Protocol. The scope of this plan includes the primary and final analyses that are planned and will be executed by the Department of Biostatistics or designee.

The analyses of PK and pharmacodynamics that will be executed by the Department of Clinical Pharmacokinetics will appear in a separate report.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCA 34176-358 Protocol Amendment 1 dated 15 NOV 2024 and CRFs approved on 07 MAY 2024. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol Amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the clinical efficacy of axatilimab in Japanese participants with cGVHD	ORR in the first 6 cycles, as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD
Secondary	
To determine other secondary measures of clinical benefit of axatilimab in Japanese participants with cGVHD	• Proportion of participants with a ≥ 7-point improvement in mLSS score • ORR, as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD • DOR, defined as the time from initial response of PR or CR until documented progression of cGVHD, start of new therapy, or death due to any cause, whichever occurs first • Organ-specific response rate based on 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD • Percent reduction in average daily dose (or equivalent) of corticosteroids • Proportion of participants who discontinue corticosteroid use after study entry
To determine the safety and tolerability of axatilimab in Japanese participants with cGVHD	• Frequency and severity of AEs, assessed by changes vital signs and ECGs and through clinical laboratory blood sample evaluations and physical and neurological examinations • Change from baseline in Karnofsky/Lansky performance status
To evaluate the axatilimab PK in plasma after treatment with axatilimab	Axatilimab PK parameters and trough plasma concentrations of axatilimab
To assess the immunogenicity of axatilimab in Japanese participants with cGVHD	Presence of antidrug antibodies

Objectives	Endpoints
[redacted]	

3. STUDY DESIGN

3.1. Overall Study Design

This is a Phase 3, open-label, multicenter study to evaluate efficacy and safety of axatilimab in Japanese participants with recurrent or refractory active cGVHD who have received at least 2 prior lines of systemic therapy.

The study will consist of the following 3 periods: screening, treatment, and follow-up. Eligible participants will receive axatilimab in 4-week (28-day) treatment cycles from Cycle 1 Day 1 until disease progression, lack of efficacy by 9 months, withdrawal of consent, or unacceptable toxicity. Disease responses will be assessed using the NIH 2014 consensus criteria (Lee et al 2015).

A primary efficacy analysis will be performed when all participants have had the opportunity to complete 6 cycles of treatment of axatilimab.

3.2. Randomization

Not applicable.

3.3. Control of Type I Error

No formal statistical tests will be performed, and 95% CIs will be provided for point estimates.

3.4. Sample Size Considerations

Approximately 20 participants will be enrolled and will receive axatilimab 0.3 mg/kg Q2W IV. Given a target response rate of 63%, the study has about 83% power to exclude a lower bound of 95% CI of 30%.

The target response rate was based on the lower boundary of ORR seen in the 0.3 mg/kg cohort in the AGAVE-201 study, which was 73.8% (95% CI: 62.7, 83.0).

The rationale of a 30% ORR threshold is as follows:

- The response rate for cGVHD in the second line and beyond is approximately 30% for all previously established treatments (Cutler et al 2017).
- In AGAVE-201, a threshold of 30% was specified.
- In the opinion of external experts involved in the clinical practice of cGVHD, 30% is considered appropriate as the threshold for this study.

3.5. Schedule of Assessments

Refer to Protocol Amendment 1 dated 15 NOV 2024 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of axatilimab is administered to the participants.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of axatilimab, unless otherwise defined. Change from baseline is defined as the postbaseline measurement minus the baseline measurement.

When scheduled assessments and unscheduled assessments occur on the same day and the time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Dates

The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

Partial cGVHD diagnosis dates will be handled as follows in the calculation:

- If only the day is missing, then the imputed day will be the last of the month.
- If both the month and day are missing, then the imputed day and month will be 31 DEC.
- No imputation will be done if the date is completely missing.

4.1.5. Cycle Length and Duration

The scheduled cycle length is 28 days for all participants in this study. Cycle 1 Day 1 is the day that the first dose of axatilimab is administered. Day 1 of subsequent cycles will correspond with the first day of administration of axatilimab in that cycle; thus, treatment cycles may become out of sync with the originally planned schedule, and the cycle length may be different from 28 days.

Treatment duration will be derived as the last dose date of axatilimab – the first dose date of axatilimab + 14 days (for Q2W dosing) or + 28 days (for Q4W dosing).

4.2. Variable Definitions

The following variables will only be calculated if not reported on the eCRF.

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

$$\text{BMI (kg/m}^2\text{)} = [\text{weight (kg)}] / [\text{height (cm)} \times 0.01]^2.$$

4.2.2. Prior/Concomitant Medication and Medical Procedure

Prior medication is defined as any nonstudy medication started before the first dose of axatilimab.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of axatilimab and is ongoing throughout the study or ends on/after the date of first axatilimab administration.
- On/after the date of first administration of axatilimab and is ongoing or ends during the course of the study.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of axatilimab. In the listing, it will be indicated whether a medication is only prior, only concomitant, or both prior and concomitant.

For prior and concomitant medications, the start/stop dates recorded in the eCRF will be used to identify when a concomitant medication was taken during the study.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

Prior medical procedures refer to procedures conducted before the first dose of axatilimab and concomitant medical procedures are procedures performed on or after the first dose.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9.4 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include but not be limited to the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

5.2. Treatment Groups

This is a single-arm study. All participants will be administered axatilimab 0.3 mg/kg Q2W IV.

5.3. Analysis Populations

5.3.1. All-Screened Population

The All-Screened Population will include all participants who signed the informed consent form.

5.3.2. Full Analysis Set

The FAS will include all participants who received at least 1 dose of study drug. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and both efficacy and safety analyses in this study.

5.3.3. Pharmacokinetic/Pharmacodynamic-Evaluable Population

The PK-Evaluable Population will include all participants who received at least 1 dose of study drug and provided at least 1 postdose plasma sample (1 PK measurement).

The Pharmacodynamic-Evaluable Population will include all participants who received at least 1 dose of study drug and provided at least 1 postdose sample (1 pharmacodynamic measurement).

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of planned tables, figures, and listings.

6.1. Demographics, Baseline Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The demographics and baseline characteristics will be summarized based on the eCRF data collection and will include but not be limited to the following: age at screening, sex, race, ethnicity, weight at baseline, height at baseline, BMI at baseline, and Karnofsky or Lansky performance status at Cycle 1 Day 1.

6.1.2. Disease History

Disease history will be summarized based on eCRF data collection and will include the number of transplants, type of conditioning, donor source, human leukocyte antigen match score, stem cell source, baseline organ involvement, and cGVHD severity if available. Additionally, key time intervals (eg, from transplant to cGVHD diagnosis and from cGVHD diagnosis to Cycle 1 Day 1) will be provided.

6.1.3. Medical History

Medical history will be coded to system organ class and preferred term using MedDRA and summarized.

6.2. Disposition of Participant

The number and percentage of participants who were treated, who were ongoing with study treatment, who completed study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, who completed the study, and who withdrew from the study with a primary reason for withdrawal will be summarized for the FAS. Screening disposition will be summarized separately for the All-Screened Population.

6.3. Protocol Deviations

Protocol deviations will be summarized and listed according to data collection.

6.4. Exposure

For all participants, exposure to axatilimab will be summarized descriptively as follows:

- **Number of cycles**: number of cycles with a nonzero dose of axatilimab. The number and percentage of participants in each duration category (eg, 0 to < 3 cycles, ≥ 3 cycles, ≥ 6 cycles) will also be summarized.
- **Time on treatment (months)**: (last dose date of axatilimab – first dose date of axatilimab + 14 days [for Q2W dosing] or + 28 days [for Q4W dosing]) / 30.4375.
- **Total number of infusions of axatilimab: t**otal number of infusions with a nonzero dose of axatilimab per participant.

- **Actual cumulative dose of axatilimab (mg):** if the entire infusion was administered, then the actual dose will be equal to the prescribed dose; if not, then the actual dose will be calculated as follows:

  (estimated volume delivered / prepared volume) × prescribed dose

  The prescribed dose will be calculated as the dose level × weight. All actual doses will then be added for the cumulative dose.

- **Planned cumulative dose of axatilimab (mg):** all prescribed doses will be added for the planned cumulative dose.
- **Actual dose intensity (mg/cycle):** total dose administered (mg) / total number of treatment cycles.
- **Relative dose intensity (%):** (actual cumulative dose / planned cumulative dose) × 100.

6.5. Prior/Concomitant Medications and Medical Procedures

Prior and concomitant medications will be coded using the WHO Drug Dictionary, and the number and percentage of participants for each medication will be summarized by WHO drug class and WHO drug term.

Prior and concomitant medical procedures will be coded to system organ class and preferred term using MedDRA. Both prior and concomitant medical procedures may be summarized descriptively.

6.6. Prior Therapy for cGVHD

Prior cGVHD therapies will be summarized by WHO drug class and WHO drug term. The number of prior therapy regimens for cGVHD will also be summarized.

Corticosteroids, calcineurin inhibitors, and mycophenolate mofetil taken as prior therapy at study entry may be allowed to continue as concomitant medications during the study. Records of these 3 drugs prior to Cycle 1 Day 1 may be summarized alongside other prior cGVHD therapies, while their exposure on or after Cycle 1 Day 1 may be summarized separately.

7. EFFICACY

Appendix A provides a list of planned tables, figures, and listings.

7.1. General Considerations

Listings of response assessments at each visit will be provided. Summary tables may be replaced with listings when appropriate. For instance, a summary table may be replaced with a listing if it only contains a few records on relatively few participants.

7.2. Efficacy Hypotheses

Not applicable.

7.3. Analysis of the Primary Efficacy Parameter

7.3.1. Primary Efficacy Analysis

The primary efficacy endpoint is ORR in the first 6 cycles, calculated based on objective response, defined as having a CR or PR at any timepoint up to Cycle 7 Day 1 and before the start of new systemic therapy for cGVHD. Early disease progression will not censor a response afterwards. Response will be assessed according to the NIH 2014 consensus criteria (Lee et al 2015). The point estimates and 95% exact binomial CIs will be provided for ORR. The primary analysis on ORR will be performed after the last participant in the FAS has either completed the Cycle 7 Day 1 assessments or has withdrawn from the study. All cGVHD assessments will be censored at the start of new systemic therapy for cGVHD. The time to first response in months will be summarized for responders. In addition, ORR at Cycle 7 Day 1 will be included as supportive analyses.

Best overall response, defined as the best response assessment assigned to a participant at any time before the start of new cGVHD therapy, will be summarized. The BOR for each participant will be determined from the overall responses in the order of CR, PR, unchanged, mixed response, and progression.

Participants with missing assessments, including participants without postbaseline response assessments, that prevent the evaluation of the primary endpoint will be considered nonresponders. No data imputation will be applied.

7.3.2. Subgroup Analyses for Primary Endpoint

Subgroup analyses may be performed on the following based on the participant's baseline status:

- Sex: Male, Female
- Age: < 17 years vs ≥ 17 years, < 65 years vs ≥ 65 years
- Number of lines of prior therapy
- Prior ibrutinib (Yes, No)
- Prior ruxolitinib (Yes, No)
- Prior belumosudil (Yes, No)

- Severity of cGVHD at screening (mild/moderate, severe)
- Number of organs involved at baseline (≤ 3 vs > 3)
- Lung involvement at baseline (Yes, No)

Subgroup analyses will only be performed if at least 5 participants are included in a subgroup. Grouping of classes may be considered if there are too few participants in some subgroups.

Subgroup analyses of the primary endpoint (ORR) will be performed in the FAS by presenting the point estimates in the subgroup with the exact 95% CIs. Summary tables and forest plots may be presented.

7.4. Analysis of the Secondary Efficacy Parameters

7.4.1. Modified Lee Symptom Score

The mLSS is a 28-item instrument comprising 7 subscales, designed to assess the impact of cGVHD on a participant's symptoms. The mLSS responders is defined as participants who achieve at least a 7-point improvement from baseline in the normalized mLSS score. This score is on a 0-100 scale, calculated as the average of the subscale scores (Lee et al 2002, Teh et al 2020). Further details are provided in Appendix B.

The proportion of mLSS responders along with 95% CIs will be presented for the first 6 cycles and throughout the study. The change from baseline will be presented by visit.

7.4.2. Overall Response Rate on Study

The ORR on study will be evaluated as a secondary endpoint. Overall response rate is defined in Section 7.3.1. Overall response rate on study with 95% exact binomial CIs and time to first response in months will be presented.

7.4.3. Duration of Response

Duration of response will be assessed for responders only and is defined as the time from the first response of PR or CR until disease progression, death for any reason, or the date of new systemic treatment for cGVHD, whichever comes first. Table 2 summarizes different situations along with the date of the event or censoring to be used in the analysis and the corresponding outcomes.

The Kaplan-Meier estimate of distribution function will be constructed for DOR. The estimated median, together with 95% CIs, will be reported. The number of participants with a response lasting for at least 20 weeks from the time of initial response may be summarized.

Table 2: Evaluation and Censoring of Duration of Response

Situation	Outcome	Date of Event or Censoring
Death without new systemic treatment or disease progression	Event	Date of death
New systemic treatment before disease progression or death	Event	Date of initiation of new systemic treatment
Disease progression before the start of new systemic treatment or death	Event	Date of the disease assessment corresponding to the disease progression
No death and no disease progression and no new systemic treatment	Censored	Date of the last disease assessment

7.4.3.1. Sensitivity Analysis

Sensitivity analyses using the following definitions for DOR may be conducted:

- DOR Sensitivity Analysis 1: DOR is defined as time from first response of either CR or PR until progression of cGVHD from nadir in organ-response level, the start of new systemic treatment, or death from any cause, whichever is earlier, in responders only (see Table 2 for censoring rules).
- DOR Sensitivity Analysis 2: DOR is defined as the time from first response of either CR or PR until the start of new systemic treatment or death, whichever is earlier. Table 3 summarizes different situations along with the date of the event or censoring to be used in the analysis and the corresponding outcomes.

Table 3: Evaluation and Censoring of Duration of Response: Sensitivity Analysis 2

Situation	Outcome	Date of Event or Censoring
Death without new systemic treatment	Event	Date of death
New systemic treatment before death	Event	Date of initiation of new systemic treatment
No death and no new systemic treatment	Censored	Last known alive date

7.4.4. Organ-Specific Response Rate

The organ-specific response rate is defined as the proportion of participants achieving either a CR or PR for each of the 9 organs assessed based on the NIH 2014 consensus criteria (Lee et al 2015). These organs include the skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs, and joints and fascia. Protocol Section 8.2.1 contains the consensus definitions of CR, PR, and progression for the assessment of organ-specific responses. The organ-specific response rate, together with 95% CIs, for each individual organ per 2014 NIH criteria will be summarized by visit, in the first 6 cycles, and on study.

7.4.5. Systemic Corticosteroid Use

Percent reductions in average daily doses (or equivalent) of corticosteroids from baseline to discontinuation of corticosteroids or Cycle 7 Day 1, whichever comes first, will be provided by 28-day time intervals. The corticosteroid dose at baseline is defined as the dose administered on Cycle 1 Day 1.

The proportion of participants who discontinue corticosteroid use after the first dose of axatilimab will also be provided by 28-day time intervals and for the first 6 cycles.

Corticosteroid doses will be converted to an equivalent dose of prednisone in mg (see Appendix C).



8. PHARMACOKINETICS AND PHARMACODYNAMICS

8.1. Pharmacokinetic Analyses

The details of the analysis methodology and results for PK assessment will be described in a separate population PK report.

8.2. Pharmacodynamic and Translational Assessments

Pharmacodynamic and translational assessments will be performed according to Tables 4 and 15 in the Protocol. The samples will be used to evaluate the effect of study drug on blood biomarkers, including circulating inflammatory mediators and phenotypic characterization of immune-cell populations.

The activity observed will be compared with the exposure of the compound. Other methods to confirm this analysis may be performed based on emerging data.

Samples will be sent from participating sites to a central laboratory for processing and storage. All analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee.

Information regarding collection, processing, and shipping of samples for laboratory assessment is provided in the Laboratory Manual.

9. SAFETY AND TOLERABILITY

Appendix A provides a list of planned tables, figures, and listings.

9.1. General Considerations

The clinical safety data (eg, vital signs, ECGs, routine laboratory tests, and TEAEs) will be summarized using descriptive statistics (eg, mean, frequency) using the FAS.

Summary tables may be replaced with listings when appropriate. For instance, a TEAE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

9.2. Adverse Events

9.2.1. Adverse Event Definitions

A TEAE is any AE, either reported for the first time or the worsening of a pre-existing event, occurring after the first dose and up to 30 days after the last dose of study drug or until the start of new cGVHD therapy. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration.

Adverse events will be tabulated by MedDRA SOC and PT. Severity of AEs will be based on NCI CTCAE v5. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Infusion-related reactions (including hypersensitivity reactions), pneumonitis, serum enzyme elevations, periorbital edema, anemia, thrombocytopenia, infections, and viral infections may be considered AEs of clinical interest and summarized separately for this study.

9.2.2. Adverse Event Summaries

An overall summary of AEs by treatment group will include the following:

- Number (%) of participants who had any TEAEs
- Number (%) of participants who had any serious TEAEs
- Number (%) of participants who had any Grade 3 or higher TEAEs
- Number (%) of participants who had any TEAEs related to study drug
- Number (%) of participants who had any serious TEAEs related to study drug
- Number (%) of participants who temporarily interrupted study drug because of TEAEs
- Number (%) of participants who permanently discontinued study drug because of TEAEs
- Number (%) of participants who had study drug dose reductions because of TEAEs
- Number (%) of participants who had any Grade 3 or higher TEAEs related to study drug
- Number (%) of participants who had any fatal TEAEs

The following summaries may be produced by MedDRA term (if 10 or fewer participants appear in a table, a listing may be appropriate):

- Summary of TEAEs by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT in decreasing order of frequency
- Summary of TEAEs by MedDRA SOC, PT, and maximum severity
- Summary of Grade 3 or higher TEAEs by MedDRA SOC and PT
- Summary of Grade 3 or higher TEAEs by MedDRA PT in decreasing order of frequency
- Summary of serious TEAEs by MedDRA SOC and PT
- Summary of serious TEAEs by MedDRA PT in decreasing order of frequency
- Summary of treatment-related TEAEs by MedDRA SOC and PT
- Summary of treatment-related TEAEs by MedDRA PT in decreasing order of frequency
- Summary of Grade 3 or higher treatment-related TEAEs by MedDRA SOC and PT
- Summary of serious treatment-related TEAEs by MedDRA SOC and PT
- Summary of TEAEs with a fatal outcome by MedDRA SOC and PT
- Summary of TEAEs of clinical interest by MedDRA SOC and PT
- Summary of Grade 3 or higher TEAEs of clinical interest by MedDRA SOC and PT

- Summary of TEAEs leading to dose interruption by MedDRA SOC and PT
- Summary of TEAEs leading to dose reduction by MedDRA SOC and PT
- Summary of TEAEs leading to study drug discontinuation by MedDRA SOC and PT

In TEAE summaries, the primary SOC will be presented alphabetically, and the PTs will be sorted within primary SOC in descending frequency.

A participant with multiple occurrences of a TEAE will be counted only once in the respective TEAE category. A participant with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. A TEAE with missing CTCAE grade will be included in the all grades column of the summary tables.

9.3. Clinical Laboratory Tests

9.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, Table 4 may be referred as tiebreaker to delineate which value will be defined as baseline.

When there are multiple nonmissing postbaseline laboratory values for a participant's particular test within a visit window, the convention described in Table 4 will also be used to determine the record used for by-visit tabulations and summaries.

Table 4: Identification of Records for Both Baseline and Postbaseline

Priority	Laboratory Visit	Proximity to Visit Window	Tiebreaker
1	Scheduled	In-window	Use smallest laboratory sequence number
2	Unscheduled	In-window	
3	Scheduled	Out-of-window	

Laboratory test values outside the normal range will be assessed for severity based on CTCAE grade or similar criteria when clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

9.3.2. Laboratory Value Summaries

All test results and associated normal ranges from laboratories will be reported in SI units. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units. For test results that will be summarized with available normal ranges, the number and percentage of participants with the laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test. This shift summary may be produced for each test. The denominator for the percentage calculation will use the number of participants in the baseline category (ie, low, high, normal, missing) during the treatment period. For numeric laboratory values, the baseline value, postbaseline value, change from baseline, and percentage change from baseline will be summarized by visit.

Shift tables will be presented showing change in CTCAE grade from baseline to worst postbaseline grade. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category.

The following summaries will be produced for laboratory data (by laboratory parameter) reported on treatment.

- The number and percentage of participants with the worst postbaseline CTCAE grade (regardless of the baseline status) will be summarized. Each participant will be counted only for the worst grade observed after baseline.
- Shift tables using CTCAE grades comparing baseline with the worst postbaseline value will be produced for hematology, chemistry, and coagulation laboratory parameters with CTCAE grades.
- For laboratory parameters for which CTCAE grades are not defined, shift tables to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.
- The number and percentage of participants meeting categorical liver function test criteria, including ALT, AST, and ALT/AST (≥ 3, 5, 8, 10, and 20 × ULN), total bilirubin (≥ 1 and 2 × ULN), ALP (≥ 1.5, 2, 3, 5, 8, and 10 × ULN), combined categories of ALT/AST and total bilirubin (eg, ALT/AST ≥ 3 × ULN and total bilirubin > ULN at the same visit and timepoint), as well as potential DILI criteria (ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and ALP < 2 × ULN at the same visit and timepoint) will be summarized. The worst values observed postbaseline for each participant will be used for each of the categories.

9.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, temperature, respiratory rate, and weight will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 5. The abnormal values for participants exhibiting clinically notable vital sign abnormalities will be listed.

Alert vital signs are defined as an absolute value outside the defined normal range and percentage change greater than 25%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be also listed.

Table 5: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24 breaths/min	< 8 breaths/min

9.5. Electrocardiograms

Twelve-lead ECGs including PR, QRS, QT, QTcB, and QTcF intervals as well as heart rate will be obtained for each participant during the study. Values at each scheduled timepoint, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of axatilimab.

Criteria for clinically notable ECG abnormalities are defined in Table 6. Electrocardiogram values will be considered alert values if the absolute percentage change from baseline is more than 25%. Participants exhibiting ECG abnormalities or alert values will be presented with study visit.

Outliers of QT, QTcB, and QTcF values, defined as absolute values > 450 milliseconds, > 480 milliseconds, > 500 milliseconds, or change from baseline > 30 milliseconds, > 60 milliseconds will be summarized by visit.

Table 6: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
PR	> 220 ms	< 75 ms
QT	> 500 ms	< 300 ms
QRS	> 120 ms	< 50 ms
QTcB, QTcF	> 480 ms	< 295 ms
HR	> 100 bpm	< 50 bpm

9.6. Physical and Neurological Examinations

All physical and neurological examinations will be listed by participant.

9.7. Karnofsky/Lansky Performance Status Scores

Karnofsky/Lansky performance status scores will be collected at timepoints as outlined in Table 3 of the Protocol. The Karnofsky scale is designed for participants aged 16 years and older, and the Lansky scale is designed for participants younger than 16 years.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 7.

Table 7: Statistical Analysis Plan Versions

SAP Version	Date
Original	03 JUN 2025

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

11. REFERENCES

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Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant 2015;21:984-999.

MDCalc. Steroid Conversion Calculator. Accessed May 22, 2025. https://www.mdcalc.com/steroid-conversion-calculator

Teh C, Onstad L, Lee SJ. Reliability and validity of the modified 7-day Lee Chronic Graft-versus-Host Disease Symptom Scale. Biol Blood Marrow Transplant 2020;26:562-567.

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the Clinical Study Report. Shells are provided in a separate document for tables that are not in the Standard Safety Tables v2.2.

The lists of tables, figures, and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard
Baseline and Demographic Characteristics			
1.1.1	Analysis Populations	FAS	X
1.1.1.1	Screening Disposition	All-Screened	
1.1.2	Summary of Participant Disposition	FAS	
1.1.3	Summary of Number of Participants Enrolled by Country and Site	FAS	X
1.1.4	Summary of Protocol Deviations	FAS	X
1.2.1	Summary of Demographics and Baseline Characteristics	FAS	
1.3.1	Summary of Disease History	FAS	
1.4.1	Summary of Prior cGVHD Therapies	FAS	
1.4.2.1	Summary of Prior Medications	FAS	X
1.4.2.2	Summary of Concomitant Medications	FAS	X
1.4.3.1	Summary of Prior Medical Procedures	FAS	X
1.4.3.2	Summary of Concomitant Medical Procedures	FAS	X
1.5.1	Summary of General Medical History	FAS	X
1.5.2	Summary of Death	FAS	X
Efficacy			
2.1.1	Summary of Overall Response in the First 6 Cycles	FAS	
2.1.2	Summary of Overall Response at Cycle 7 Day 1	FAS	
2.1.3	Summary of Overall Response on Study	FAS	
2.2.1	Summary of Duration of Response	FAS	
2.2.2	Summary of Duration of Response: Sensitivity Analysis 1	FAS	
2.2.3	Summary of Duration of Response: Sensitivity Analysis 2	FAS	
2.3.1	Summary of Responders Based on the Normalized mLSS	FAS	
2.3.2	Summary of Change From the Baseline of the Normalized mLSS	FAS	
2.4.1	Summary of Organ-Specific Response by Visit	FAS	
2.4.2	Summary of Organ-Specific Response in the First 6 Cycles	FAS	
2.4.3	Summary of Organ-Specific Response on Study	FAS	
Safety			
3.1.1	Summary of Exposure and Duration of Exposure to Axatilimab	FAS	
3.1.2	Summary of Exposure to Systemic Corticosteroids by Time Interval in the First 6 Cycles	FAS	
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	FAS	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS	X

Table No.	Title	Population	Standard
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	X
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	FAS	X
3.2.5	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.6	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	X
3.2.7	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.8	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	X
3.2.9	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.10	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	X
3.2.11	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.12	Summary of Serious Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.13	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.14	Summary of Treatment-Emergent Adverse Events of Clinical Interest by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.15	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events of Clinical Interest by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.16.1	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.16.2	Summary of Treatment-Emergent Adverse Events Leading to Dose Reduction by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.16.3	Summary of Treatment-Emergent Adverse Events Leading to Axatilimab Discontinuation by MedDRA System Organ Class and Preferred Term	FAS	X
3.3.1.1	Summary of Laboratory Values - Hematology	FAS	X
3.3.1.2	Summary of Laboratory Values - Chemistry	FAS	X
3.3.1.3	Summary of Laboratory Values - Coagulation	FAS	X
3.3.2.1	Shift Summary of Hematology Laboratory Values - to the Worst Abnormal Value	FAS	X
3.3.2.2	Shift Summary of Chemistry Laboratory Values - to the Worst Abnormal Value	FAS	X
3.3.2.3	Shift Summary of Coagulation Laboratory Values - to the Worst Abnormal Value	FAS	X
3.3.3.1	Shift Summary of Hematology Laboratory Values in CTCAE Grade - to the Worst Abnormal Value	FAS	X

Table No.	Title	Population	Standard
3.3.3.2	Shift Summary of Chemistry Laboratory Values in CTCAE Grade - to the Worst Abnormal Value	FAS	X
3.3.3.3	Shift Summary of Coagulation Laboratory Values in CTCAE Grade - to the Worst Abnormal Value	FAS	X
3.3.4.1	Treatment-Emergent Worsening of Laboratory Abnormalities - Hematology	FAS	X
3.3.4.2	Treatment-Emergent Worsening of Laboratory Abnormalities - Chemistry	FAS	X
3.3.4.3	Treatment-Emergent Worsening of Laboratory Abnormalities - Coagulation	FAS	X
3.3.5	Summary of Liver Chemistry	FAS	X
3.4.1	Summary of Systolic Blood Pressure	FAS	
3.4.2	Summary of Diastolic Blood Pressure	FAS	
3.4.3	Summary of Pulse	FAS	
3.4.4	Summary of Respiration Rate	FAS	
3.4.5	Summary of Body Temperature	FAS	
3.4.6	Summary of Body Weight	FAS	
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	FAS	X
3.5.2	Summary of QRS Interval (ms) From 12-Lead ECG	FAS	X
3.5.3	Summary of QT Interval (ms) From 12-Lead ECG	FAS	X
3.5.4	Summary of QTcF Interval (ms) From 12-Lead ECG	FAS	X
3.5.7	Summary of Heart Rate From 12-Lead ECG	FAS	X
3.5.8	Summary of Outliers of QT, QTcB, and QTcF Interval Values (ms) From 12-Lead ECG	FAS	X
3.6.1	Summary of Karnofsky/Lansky Performance Status Scores by Visit	FAS	
3.8.1	Summary of Bone Turnover Markers and Bone Density Scan Values	FAS	

Figures

Figure No.	Title
4.1.1	Forest Plot of Overall Response and 95% CI

Listings

Listing No.	Title
2.1.1	Participant Enrollment and Disposition Status
2.2.1	Participant Inclusion and Exclusion Criteria Violations
2.2.2	Protocol Deviations
2.3	Analysis Populations
2.4.1	Demographic and Baseline Disease Characteristics
2.4.2.1	Cancer History
2.4.2.2	Allogeneic Hematopoietic Stem Cell Transplant History
2.4.3	Prior cGVHD Therapies
2.4.5	Medical History
2.4.6	Prior and Concomitant Medications
2.4.7	Prior and Concomitant Medical Procedures
2.5.1	Axatilimab Exposure

Listing No.	Title
2.5.2	Systemic Corticosteroid Exposure
2.5.3	Concomitant Calcineurin Inhibitor Exposure
2.5.4	Concomitant Mycophenolate Mofetil Exposure
2.6.1	Overall Response in the First 6 Cycles
2.6.2	Overall Response on Study
2.6.3	Death
2.6.4	Organ-Specific and Overall Response by Visit
2.6.5	Modified Lee Symptom Score by Visit
2.6.6	Duration of Response
2.6.7	Duration of Response: Sensitivity Analysis 1
2.6.8	Duration of Response: Sensitivity Analysis 2
2.7.1	Adverse Events
2.7.2	Treatment-Emergent Adverse Events Related to Study Drug
2.7.3	CTCAE Grade 3 or Higher Adverse Events
2.7.4	Adverse Events Leading to Dose Modification
2.7.5	Serious Adverse Events
2.7.6	Fatal Adverse Events
2.7.7	Adverse Events Leading to Study Drug Discontinuation
2.7.8	Adverse Events Leading to Study Drug Interruptions or Delays
2.8.1.1.1	Clinical Laboratory Values - Hematology
2.8.1.1.2	Clinical Laboratory Values - Chemistry
2.8.1.1.3	Clinical Laboratory Values - Coagulation
2.8.1.1.4	Clinical Laboratory Values - Urinalysis
2.8.1.1.5	Clinical Laboratory Values - Liver Chemistry
2.8.1.1.6	Clinical Laboratory Values - Pregnancy
2.8.1.2.1	Abnormal Clinical Laboratory Values - Hematology
2.8.1.2.2	Abnormal Clinical Laboratory Values - Chemistry
2.8.1.2.3	Abnormal Clinical Laboratory Values - Coagulation
2.8.1.3.1	Clinical Laboratory Values With Toxicity Grade >= 3 - Hematology
2.8.1.3.2	Clinical Laboratory Values With Toxicity Grade >= 3 - Chemistry
2.8.2.1	Vital Signs
2.8.2.2	Abnormal Vital Sign Values
2.8.2.3	Alert Vital Sign Values
2.8.3.1	12-Lead ECG Values
2.8.3.2	Abnormal 12-Lead ECG Values
2.8.3.3	Alert 12-Lead ECG Values
2.9.1	Physical Examinations
2.9.2	Neurological Examinations
2.9.3	Karnofsky/Lansky Performance Status Score
2.9.4	Bone Turnover Markers and Bone Density Scan Values
2.9.5	Pulmonary Function Tests

APPENDIX B. MODIFIED LEE SYMPTOM SCORE

The mLSS is a participant-reported outcome measure including the following 7 subscales: skin, eyes, mouth, lung, nutrition, energy, and psych (Lee et al 2002, Teh et al 2020). Details are shown in Table B1.

Subscale scores can be calculated if at least 50% of the items in the subscale are completed, and the normalized mLSS can be calculated if at least 50% of the subscale scores are calculated. The item scores range from 0 to 4 (not at all, slightly, moderately, quite a bit, extremely). A linear transformation is applied to obtain a 0-100 scale, where 0 indicates that all answered items were a "0," and 100 indicates that all answered items were a "4."

Subscale scores will be calculated as

$$Subscale\ Score = (I_1 + I_2 + \cdots + I_n) \times 25 / n$$

where I_1, I_2, $\cdots$, and I_n are the scores of items included in a subscale and n is the number of questions (items) being answered within a subscale.

Missing items will not be included in the scoring. The normalized mLSS will be calculated as the average of the subscale scores.

Table B1: Scoring Algorithm for the mLSS

Subscale Name	Number of Items	Items
Skin	5	a. Abnormal skin color b. Rashes c. Thickened skin d. Sores on skin e. Itchy skin
Eye	3	f. Dry eyes g. Need to use eye drops frequently h. Difficulty seeing clearly
Mouth	2	i. Need to avoid certain foods due to mouth pain j. Ulcers in mouth
Lung	4	k. Frequent cough l. Colored sputum m. Shortness of breath at rest n. Fevers
Nutrition	4	o. Difficulty swallowing solid foods p. Difficulty swallowing liquids q. Vomiting r. Weight loss
Energy	7	s. Shortness of breath with exercise t. Joint and muscle aches u. Limited joint movement v. Muscle cramps w. Weak muscles x. Loss of energy y. Need to sleep more/take naps
Psych	3	z. Depression aa. Anxiety bb. Difficulty sleeping

APPENDIX C. SYSTEMIC CORTICOSTEROID USE

Participants may receive different types of corticosteroids through IV or PO routes, with varying units and frequencies. To evaluate systemic steroid use for cGVHD, the doses and units of the corticosteroids will be standardized by converting them to prednisone equivalents as shown below.

Systemic Prednisone Equivalent Dose Conversion

Medication	Route	Equivalent Dose (mg)	Prednisone Equivalent Factor
Betamethasone	IV	0.75	6.7
Cortisone	PO	25	0.2
Dexamethasone	IV or PO	0.75	6.7
Hydrocortisone	IV or PO	20	0.25
Methylprednisolone	IV or PO	4	1.25
Prednisolone	PO	5	1
Prednisone	PO	5	1
Triamcinolone	IV	4	1.25

Source: MDCalc 2025.

The prednisone equivalent conversion factor will be calculated by dividing the equivalent dose for prednisone by the equivalent dose for each medication. The systemic prednisone equivalent dose will be calculated by multiplying the dose by the prednisone equivalent conversion factor.